Twitter Thread by Kevin Bass, MS

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In a new clinical trial with 145 subjects, subjects were given drinks sweetened with aspartame, glucose, fructose, or high-fructose corn syrup for two weeks.

Some results
HFCS group:
17% higher LDL-C
15% higher apoB
11% higher

Subjects were given beverages to drink three times per day, containing:

Aspartame, control
Glucose, 25% daily energy requirements
Fructose, 17.5%
Fructose, 25%
High-fructose corn syrup, 17.5%
HFCS, 25%
Sucrose, 25%

2.3. Group assignment

Assignment to the groups was not randomized; the experimental groups were matched for sex, BMI, and concentrations of fasting triglyceride (TG), cholesterol, HDL-C, and insulin in plasma collected during the in-person interviews. The study included eight experimental groups with a total of 187 participants and was designed to compare the metabolic effects of consuming beverages sweetened with Asp (non-caloric control), glucose (25% ereq (G25)), fructose (25% (F25) and 17.5% ereq (F17.5)), HFCS (25% (HFCS25), 17.5% (HFCS17.5) and 10% ereq) and sucrose (25% ereq). We previously reported data from 16 of 28 participants from each of 3 groups (F25G25 and HFCS25) [6] and the data from 4 groups (Asp, 10% ereq HFCS, HFCS17.5 and HFCS25) [8].

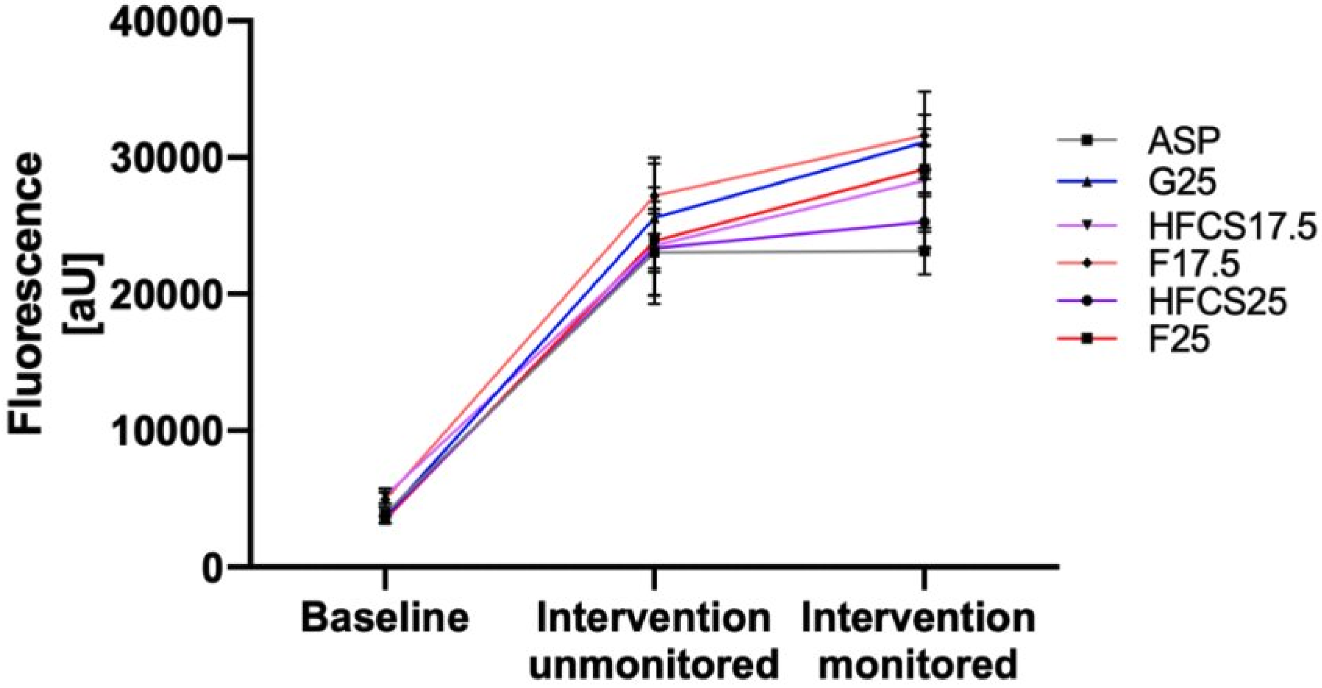
Patients were told to refrain from drinking any other sugar-sweetened beverages.

Riboflavin was added to the drinks as a biomarker for adherence and tested in the urine.

2.4. Study beverages

All beverages were prepared by the study staff. Sugar-sweetened beverages were flavored with an unsweetened drink mix (Kool-Aid; Kraft Foods, Northfield, IL) in addition to the respective sugar. Asp-sweetened beverages contained a fruit-flavored drink mix (Market Pantry®, Target, Minneapolis, MN). The sugar-sweetened beverages contained glucose (STALEYDEX® crystalline dextrose, Tate & Lyle, Hoffman Estates, IL, USA), fructose (KRYSTAR® crystalline fructose, Tate & Lyle, Hoffman Estates, IL, USA), or HFCS (ISOSWEET® 5500, Tate & Lyle, Hoffman Estates, IL, USA). These beverages were formulated by a designated staff person with the 25% ereq beverages containing 15% sugar in water (weight/weight). The amount of beverage provided (mean ± SE for all subjects: 1081 ± 12 g divided into three servings) was standardized among the 6 groups and based on individual energy requirements. During the outpatient phase, the subjects were instructed to drink three servings per day of the provided beverages, to consume their usual diet, and to refrain from consuming other sugar-containing beverages, including fruit juice. To monitor compliance, a biomarker (riboflavin) was added to the beverages and fluorometrically measured in urine samples [8]. Subjects were informed that they were being monitored to ensure beverage consumption, but were not provided details about the method. Urinary riboflavin was assessed in urine samples collected during baseline, during the middle and end of outpatient intervention, and during inpatient intervention.

Urinary riboflavin was low at the beginning, rose throughout the study, and did not rise differently between participants in each group over the course of the study, indicating that the biomarker worked and adherence was similar between groups.



The trial was double-blinded and on an outpatient basis.

Subjects were not randomized but groups were matched for sex, BMI, and concentrations of fasting triglyceride (TG), cholesterol, HDL-C, and insulin at baseline.

2.3. Group assignment

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Correspondingly, the groups were roughly matched for the means of these parameters. This is important because differing baseline metabolic characteristics could skew results between groups, so matching them minimizes this bias.

Table 1
Baseline anthropometric and metabolic parameters.

	Aspartame-0%	Glucose-25%	HFCS-17.5%	Fructose-17.5%	HFCS-25%	Fructose-25%
No. of participants	23	28	16	22	28	28
Female (%)	12 (52.2)	13 (46.4)	9 (56.2)	11 (50)	13 (46.4)	13 (46.4)
Age, y	25 ± 6	26 ± 6	24 ± 5	26 ± 5	27 ± 7	27 ± 6
BMI, kg/m^2	24.8 ± 3.3	25.8 ± 3.4	24.2 ± 3.3	24.8 ± 4.4	24.9 ± 4.0	25.4 ± 3.7
Body fat, %	27.0 ± 9.8	28.9 ± 8.4	25.9 ± 9.6	27.0 ± 9.7	26.0 ± 9.7	29.0 ± 10.3
Waist circumference, cm	75.2 ± 6.4	79.0 ± 9.3	73.3 ± 7.7	76.3 ± 10.8	77.0 ± 10.1	78.3 ± 10.2
Fst glucose, mmol/L	5.02 ± 0.37	4.99 ± 0.34	4.98 ± 0.34	4.96 ± 0.34	5.03 ± 0.35	5.02 ± 0.4
Fst insulin, pmol/L	87.9 ± 37.9	88.8 ± 30.7	81.7 ± 19.3	93.2 ± 31	90.4 ± 35.8	102.5 ± 68.4
Fst TG, mmol/L	1.14 ± 0.59	1.15 ± 0.53	1.1 ± 0.39	1.39 ± 0.52	1.22 ± 0.57	1.12 ± 0.39
Fst C, mmol/L	3.86 ± 0.66	4.19 ± 0.8	4.27 ± 0.9	4.21 ± 0.77	4.08 ± 0.89	3.9 ± 0.64
Fst HDL-C, mmol/L	1.02 ± 0.19	1.18 ± 0.39	1.2 ± 0.24	1.1 ± 0.2	1.18 ± 0.36	1.15 ± 0.24
Fst LDL-C, mmol/L	2.17 ± 0.6	2.39 ± 0.78	2.42 ± 0.85	2.39 ± 0.64	2.37 ± 0.71	2.16 ± 0.64
Fst uric acid, μmol/L	272.1 ± 62.4	283.9 ± 65.5	261.9 ± 47.7	278.7 ± 54.9	270.6 ± 69.7	268.8 ± 57.5

Abbreviations: BMI = body mass index; fst = fasting; TG = triglycerides; C = cholesterol.
Conversion factors: To convert glucose to mg/dL, divide by 0.0555; insulin to μU/mL, divide by 6.945; triglycerides to mg/dL, divide by 0.0113; cholesterol to ml/dL, divide by 0.0295 uric acid to ml/dL divide by 59.485.
Values are mean ± SD.

There were minimal dropouts in each group. Minimal dropouts means that something from the intervention did not cause people to drop out and the results to be artificially biased.

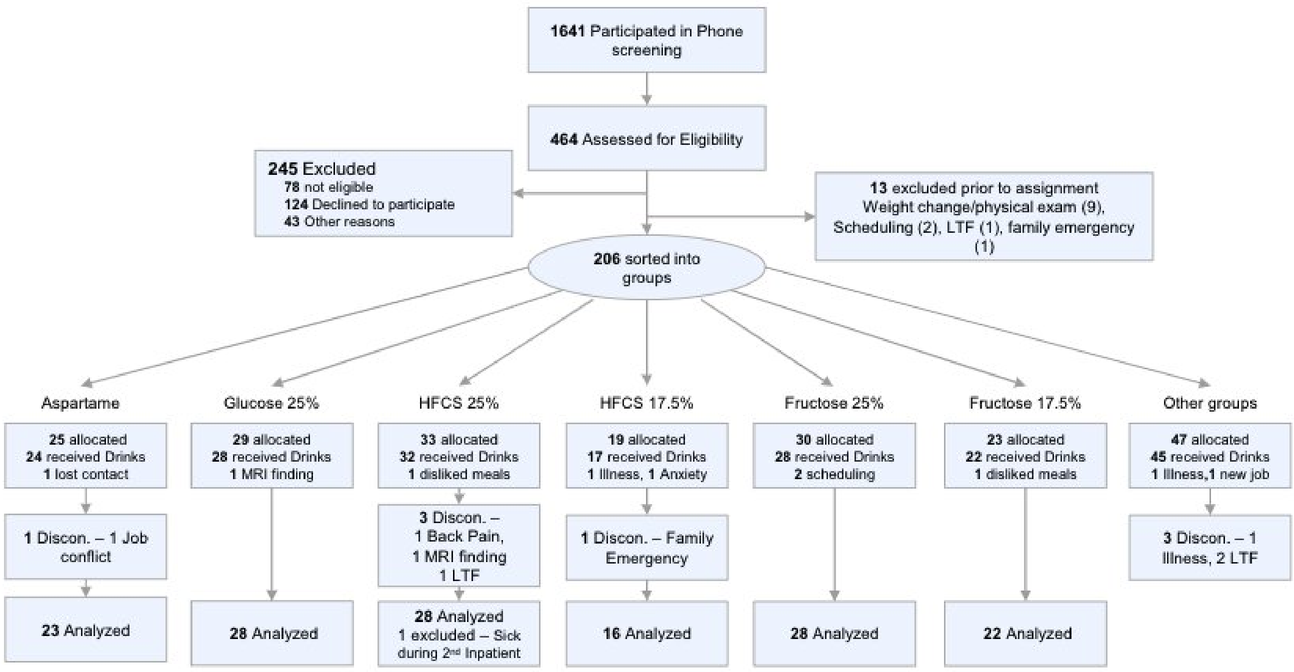


Fig. 1. Trial profile. LTF – lost to follow-up; Discon. – discontinued participation.

There was no significant increase in bodyweight over the course of the study, meaning that the results found could not be caused by a change in bodyweight.

Table 2
Body weight and plasma concentrations of risk factors at baseline and adjusted difference after consuming Aspartame or sugar-sweetened beverages for two weeks.

	Aspartame	Glucose-25%	HFCS-17.5%	Fructose-17.5%	HFCS-25%	Fructose-25%	effect of	Total variation accounted for in % [95% CI][a]	p-value
Body weight, kg									
Baseline	71.8 ± 10.6	75.5 ± 12.8	69.9 ± 14.3	72.5 ± 15	72.9 ± 14.5	75.7 ± 12.9			
Δ	−0.03	0.56	0.32	0.02	0.79	0.07	sugar	6.55% [0.00% to 12.65%]	0.090
[95% CI]	[−0.53 to 0.47]	[0.11 to 1.02]	[−0.28 to 0.92]	[−0.49 to 0.53]	[0.34 to 1.24]	[−0.38 to 0.53]	sex	0.60% [0.00% to 5.43%]	0.347

A before-after comparison was used, with aspartame as a control.

All fructose-containing drinks increased:
24-hour triglycerides
24-hour uric acid
Fasting LDL cholesterol
Fasting apoB

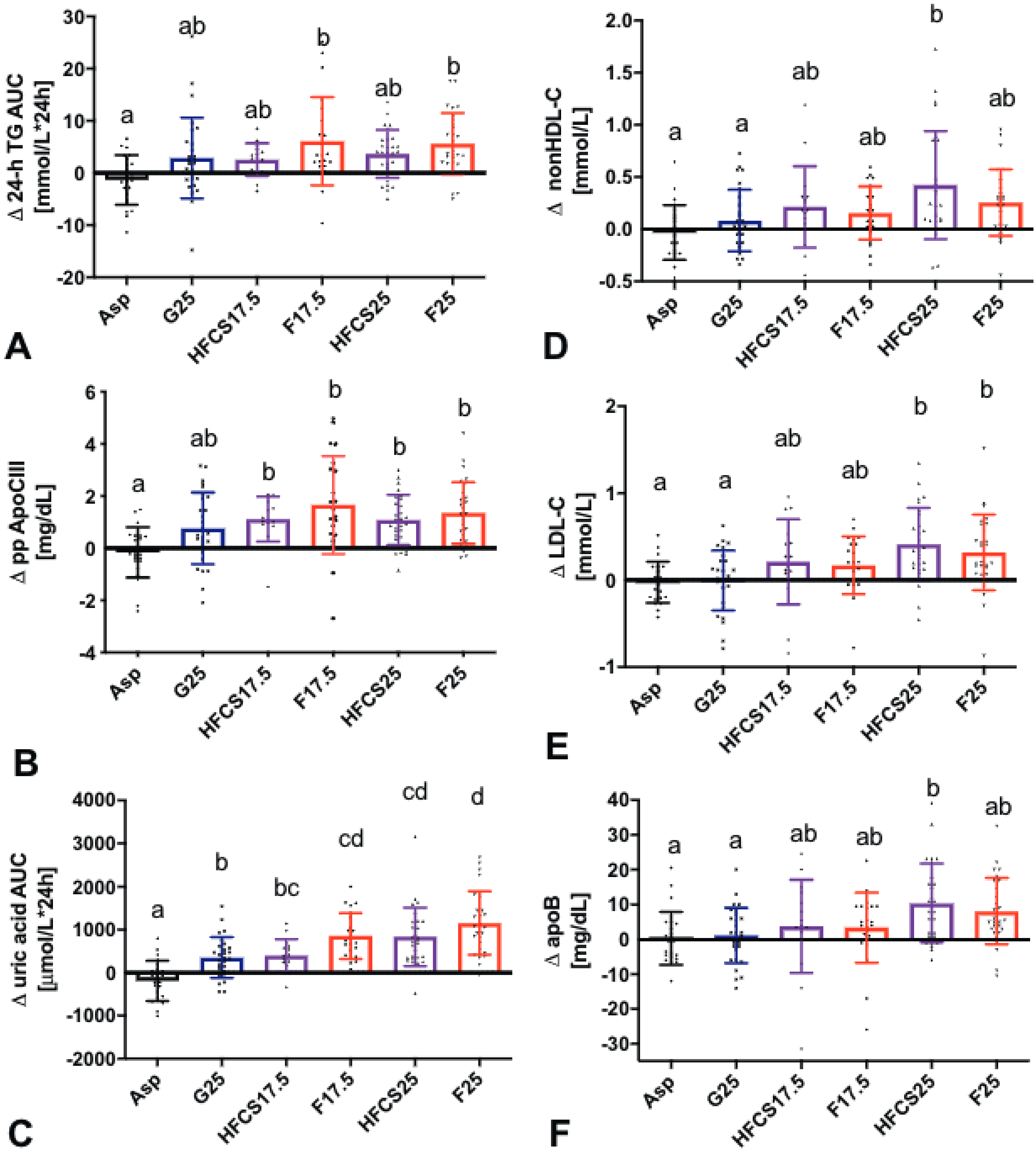
The increases in each category were:

24h triglycerides: Fructose > HFCS & glucose
Fasting LCL-C: F25 & HFCS25 > F17.5 & HFCS17.5
Fasting apoB: F25 & HFCS25 > F17.5 & HFCS17.5
24h uric acid: F25 > HFCS25 & F17.5 > HFCS17.5 > G25

FRUCTOSE-SWEETENED BEVERAGES BAD

The graph is as follows. All bars with different subscripts are significantly different from each other.

FRUCTOSE-SWEETENED BEVERAGES BAD



Even though the groups being tested have only a relatively small number of subjects (about 20-30), the dose-response relationship for some of the parameters increases our confidence that the effects are real.

FRUCTOSE-SWEETENED BEVERAGES BAD

As you can see, glucose only increased uric acid, triglycerides, and apoCIII (present on the major energy-containing lipoproteins in the blood), not lipoproteins.

However, HFCS, containing both fructose and glucose, often had a more potent effect than fructose alone.

This is interesting, because it suggests that glucose and fructose interact to worsen metabolic parameters.

The investigators measured this interaction in post-hoc analyses and found that the interaction between glucose and fructose accounted for a substantial proportion of the effect not accounted by glucose or fructose alone.

Table 3
Variation accounted for by fructose, glucose or their combination on measured outcomes.

	Total variation accounted for in % [95% CI]	*P*-value
Fasting nonHDL-C		
F	4.97% [0.4% to 11.3%]	0.002
G	0.75% [0.0% to 5.9%]	0.209
F*G	5.86% [0.7% to 14.6%]	0.002
Postprandial nonHDL-C		
F	11.20% [10.6% to 21.3%]	<0.0001
G	1.58% [1.1% to 7.7%]	0.062
F*G	5.39% [4.9% to 13.9%]	0.002
Fasting LDL-C		
F	5.84% [0.7% to 14.5%]	0.001
G	0.08% [0.0% to 3.3%]	0.661
F*G	6.17% [0.8% to 15.0%]	0.001
Postprandial LDL-C		
F	4.01% [0.1% to 11.9%]	0.006
G	0.46% [0.0% to 5.0%]	0.306
F*G	8.43% [1.8% to 18.0%]	0.0002
Fasting apoB		
F	4.44% [0.2% to 5.6%]	0.004
G	0.34% [0.0% to 0.5%]	0.396
F*G	4.51% [0.3% to 12.6%]	0.005
Postprandial apoB		
F	6.64% [1.0% to 15.6%]	0.001
G	1.37% [0.0% to 7.3%]	0.099
F*G	5.21% [0.4% to 13.7%]	0.003
24-h TG AUC		
F	10.90% [3.1% to 21.0%]	<0.0001
G	2.30% [0.0% to 9.1%]	0.049
F*G	0.42% [0.0% to 4.9%]	0.340
Postprandial apoCIII		
F	11.67% [3.6% to 21.9%]	<0.0001
G	1.94% [0.0% to 8.4%]	0.064
F*G	0.03% [0.0% to 2.5%]	0.8099
24-h uric acid AUC		
F	32.72% [20.6% to 43.3%]	<0.0001
G	4.82% [0.3% to 13.1%]	0.001
F*G	0.00% [0.0% to 0.8%]	0.943
Fasting ox.LDL[a]		
F	0.57% [0.0% to 6.5%]	0.384
G	0.45% [0.0% to 6.1%]	0.538
F*G	15.26% [4.7% to 27.6%]	<0.0001

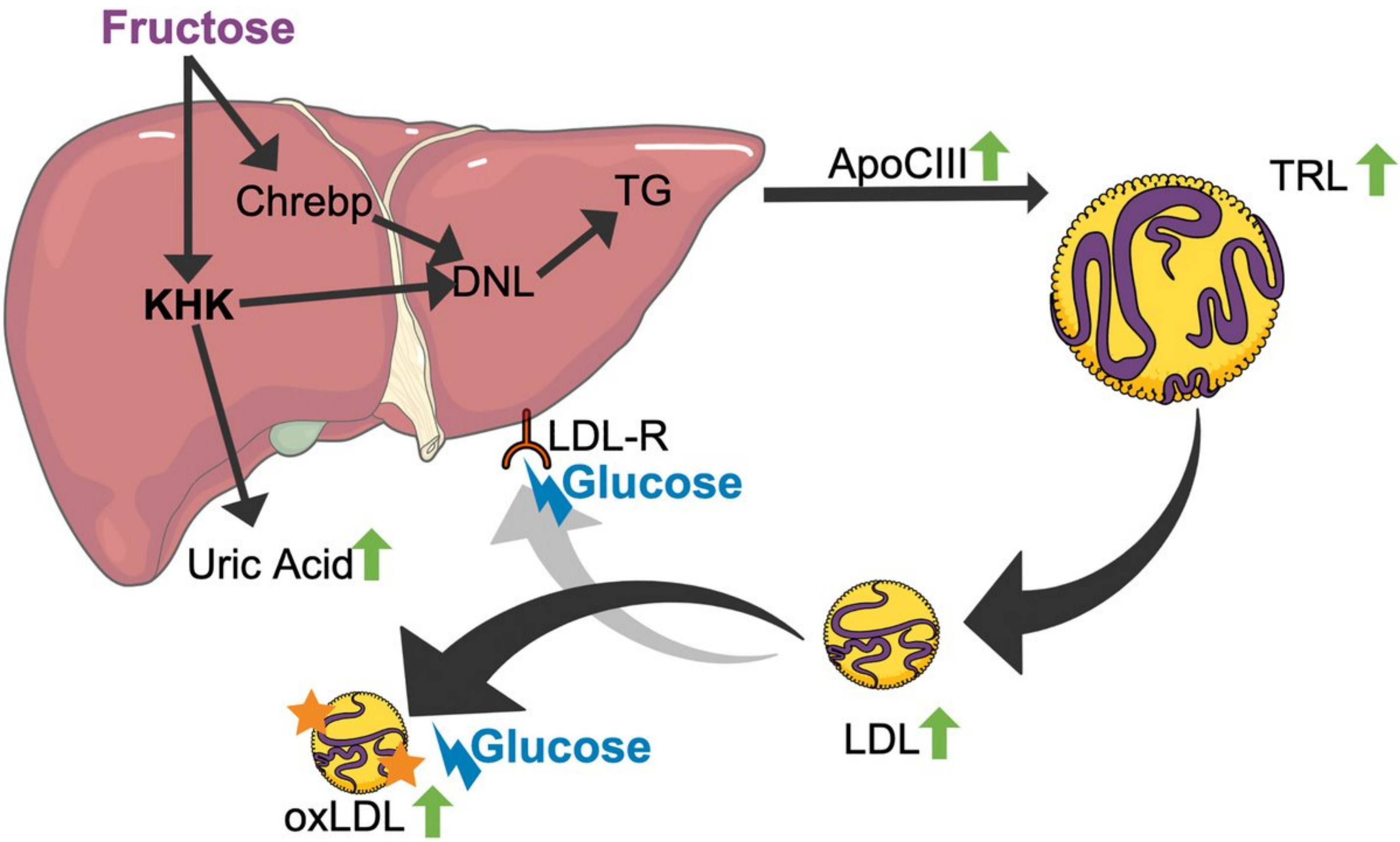
Data were estimated from Mulivariate regression model (fructose, glucose, fructose*glucose) adjusted for outcome at Baseline and sex.
F- fructose, G – glucose.[a]
[a] excluding groups HFCS17.5 and F17.5

In other words:

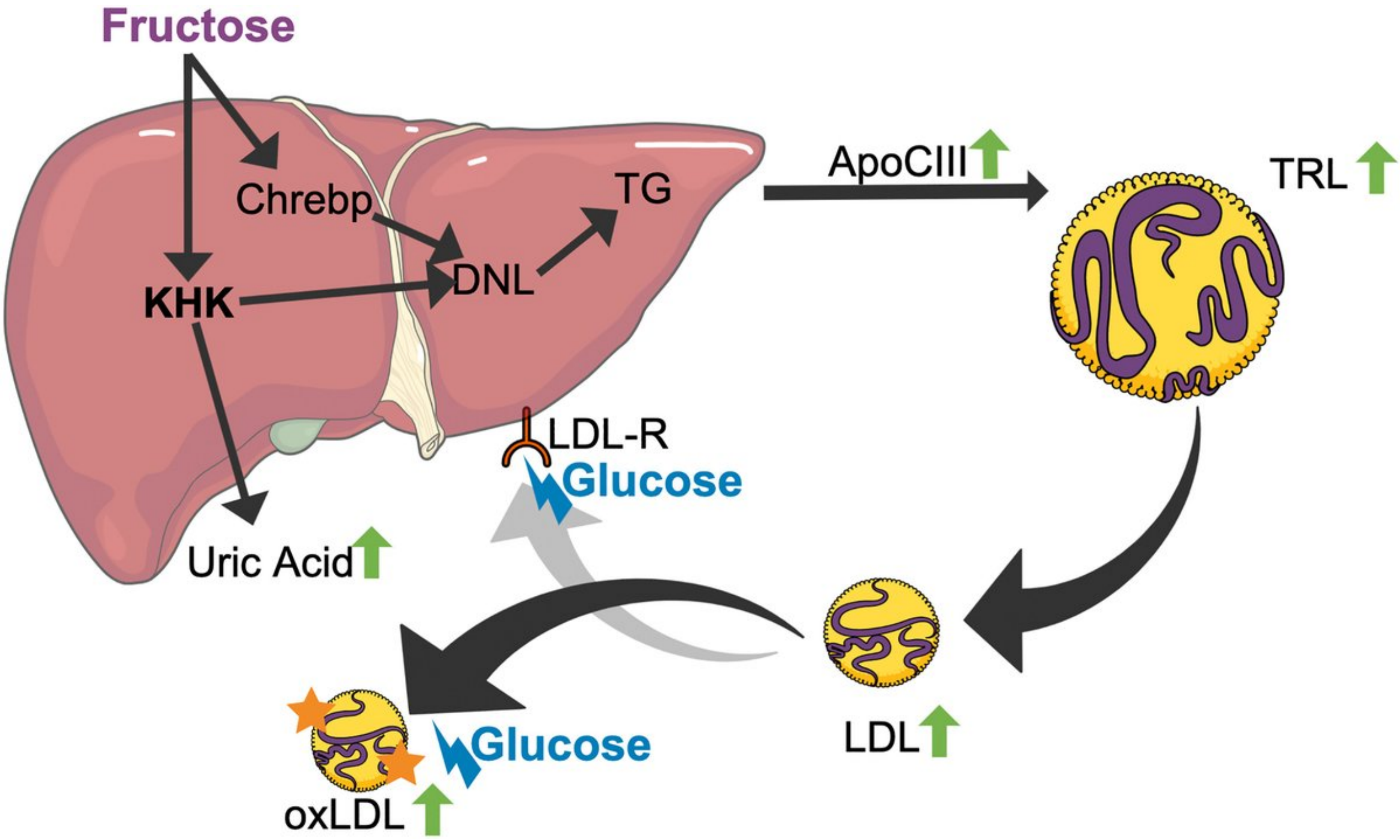
Fructose by itself is bad.
Glucose is either not bad or not very bad.
But fructose plus glucose are horrible.

This is important because fructose plus glucose is the main form of dietary sweetener in the Western diet. In other words, horrible.

The study authors account for this in the following hypothetical model, supported by other research.



In this model (to simplify somewhat), fructose increases secretion of energy-containing TG-rich lipoproteins (TRLs), which then become LDL after the energy in the TRLs is used. Glucose blocks the uptake of LDL by the liver and encourages oxidation in the blood.



This is just a hypothetical model, so please do not bandy it about for the next 10 years on Twitter as if it is the truth (as many of you are prone to do, ugh), or I will personally kill you.

(This is a joke. I will not kill anyone @TwitterSupport.)

Takeaways

1. Consumption of fructose-containing beverages increases factors that contribute to heart disease, dementia, etc., in a dose-response manner. This means soft drinks, sweetened teas, etc.

Two bottles of Coca-Cola would get many people to a similar dose as this study.

Even if you maintain a healthy weight, you will still increase these risk factors if you consume sugar-sweetened beverages.

In other words, sugar-sweetened beverages and saturated fat have very similar effects on lipoproteins involved in heart disease risk: bad.

2. Sugar is not sugar. Glucose and fructose are metabolically different, so your bread, even if it was liquid (and it is not--more in a moment), is not the same as Coca-Cola.

Stop saying all carbs are sugar.

Link this thread to anyone who says all carbs are sugar. They aren't.

3. This isn't directly addressed by this study, but cane sugar has the same metabolic effects as high-fructose corn syrup. Don't think it is any different, because it is not.

Caveats.

This was in sugar-sweetened beverages, not in foods.

Fruit does not have the same effects as a Coca-Cola, so don't even.

And bread does not have the same effects as glucose, either. So. Do. Not. Even.

The findings of this study also need to be replicated.

For people digging into this study, just note that some of the figures in table 2 are broken. Yes, I am aware of it. not sure why, but you can figure out what the actual figures are by using the CIs. This should still probably be corrected by the journal.

This is how you tweet about studies on Twitter.

Teach, don't propagandize.

What would be nice is if Twitter had a feature that gave users ready access to the "best take" on any given study, attached as a link to any tweet of that study, so that bad actors could not readily distort everything that comes out. Smash down all echo chambers. Restore sanity.

Thanks for reading. If you like my stuff, please become my patron or send a one-time donation. Every contribution makes a big difference.

https://t.co/Hk08sIg7lK

Addendum 1

Yes most “sugar-sweetened” beverages are sweetened with high-fructose corn syrup. This is glucose + fructose.

Some are sweetened with just sucrose, aka table sugar. Sucrose is also glucose + fructose.

Almost everything that is sweetened and does not use an artificial sweetener is sweetened with glucose + fructose.

In contrast, starchy carbohydrates are broken into only glucose.

Critical distinction.

Addendum 2

Liquids are metabolized differently than solid foods because solid foods must be broken down before they are absorbed.

This means they are absorbed more slowly and further down the GI tract.

So the speed of absorption changes with solid foods, which changes the body’s response to these foods.

Furthermore, because the GI tract is a hormone-secreting organ, absorption lower in the GI tract will change hormonal signaling and thus change the body’s metabolic response.

These two reasons are why we cannot confidently extrapolate from this study to solid foods containing fructose. We need separate studies to know the metabolic/lipoprotein effects of such foods. Other data indicate that solid foods do not cause these effects.

Addendum 3

This was a very similar design to a study that found very similar results

Now I feel confident with these results

Don’t drink sugary drinks kids https://t.co/1XcpDeS41o

> This is a very similar study with similar results https://t.co/NQkSUwurUs pic.twitter.com/omO12ZqsgQ
>
> — Jacob Gudiol (@JacobGudiol) January 18, 2021

Addendum 4 (don't you like how I am numbering my addenda all official-like?)

Getting this question a lot.

https://t.co/SnlCeODtge

I don't believe there is yet a clear answer, unfortunately. I have included some screenshots from a recent review.

https://t.co/nWf9sF0I8N

5.2. Intervention Studies

5.2.1. Absence of Effect

A meta-analysis of 19 randomized controlled trials investigating the effects of various fruit juices, concentrated fruit juices, and fruit juice powders suggested that fruit juices had a borderline significant effect on the reduction of diastolic blood pressure and did not affect total or LDL-C [85]. However, nearly all these studies investigated a dose of free sugars provided by fruit juices well below 10% Ereq, whereas adverse effects in relation to the consumption of sugar-sweetened beverages and blood lipids have never been observed at doses below 10% Ereq. Moreover, very few studies included in the meta-analysis directly compared the effects of fruit juices to sugar-sweetened beverages. The interventions were all conducted with usual diets with or without restrictions of consuming other fruits juices, alcohol, food sources of antioxidants, and specific fruits and vegetables. None of the 19 studies included in the meta-analysis controlled for energy intake nor for macronutrient distribution. In a 12-week trial, Simpson et al. (2016) showed that the consumption of 250 mL/day of natural orange juice in overweight hypercholesterolemic men did not affect body weight, insulin sensitivity, and circulating lipids when compared to the consumption of energy-matched orange sugar-sweetened beverage [86]. Nevertheless, a 250 mL dose of fruit juice provides 25 g of total free sugars [25], which represents an average of only 5% Ereq.

> So would you expect a juiced fruit, in a blender or esp in a juicer, to resemble the Fructose-only groups in this study or is that also way too different?
>
> — Tak (@LouferTak) January 18, 2021

Suffice to say that whole fruits are probably a better bet.

Yet this does not necessarily mean that blended fruits are bad. We don't know. But if you want to hedge your bets, until we have more data, it wouldn't be a bad idea to focus on whole fruits over blended or fruit juice.