Detailed Study Notes

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Introduction to this Episode

There is almost universal agreement that excess added sugar in the diet is detrimental to health. However, much of this negative health impact clearly relates to the ability of high sugar intakes to drive excess calorie intake and fat accumulation, which cause health issues.

But what about situations where there is not a calorie surplus (hypercaloric diet) or weight gain?

Some people claim that sugar is inherently damaging. While others push back and claim sugar is only a problem in the context of a hypercaloric diet.

So which position is more accurate? What evidence do we have?

In this episode, Dr. Alan Flanagan and Danny Lennon take a look at situations of eucaloric (or even hypocaloric) diets, and what impact sugar has.

Specifically, they investigate: in a situation where someone is not overconsuming calories or gaining weight, what health impacts do added sugars have? And if there are these calorie-independent effects, at what thresholds do they occur?

Connection to Previous Episodes

#242: Jake Mey, PhD, RD – How Much Sugar is Too Much?

- In this episode we discuss whether sugar has detrimental health effects if there is no weight gain.
- Dr. Mey brings up one of the studies on whole grains vs. refined grains, that we discussed in the present episode.
- We also get into the question of how much sugar counts as a 'high intake'?
- You can find this episode here.

#155: Kimber Stanhope, PhD – Effects of Sugar Consumption on Body Composition, Lipid Regulation and Insulin Sensitivity

- Dr. Kimber Stanhope of UC Davis discusses the scientific research that exists on sugar consumption and its effect on health and body composition.
- Her work focuses on investigating the effects of sugar consumption on the development of metabolic disease, utilizing well-controlled diet intervention studies in human subjects.
- The discussion also gets into fat accumulation at the liver and the differing metabolic effects of consuming different types of sugars (e.g. fructose, glucose, sucrose)
- You can find this episode here.

#76: Nicole Avena, PhD – Hedonic Eating, Food Reward & Claims About "Sugar Addiction"

- Neuroscientist Nicole Avena, PhD was on the podcast to discuss hedonic eating vs. caloric need, and whether there is evidence behind concepts like "food addiction" and "sugar addiction".
- Dr. Avena received a Ph.D. in Neuroscience and Psychology from Princeton University, followed by a postdoctoral fellowship in molecular biology at The Rockefeller University in New York City.
- You can find this episode here.

Sigma Articles

- In the current episode we discuss the impact of sugar intake on NAFLD. To get a deeper background on the evidence around diet and NAFLD, you can read our Sigma Statement titled: '*Fatty Liver: The Relationship Between Diet & NAFLD*'

Setting the Stage

- *"**Excess** sugar is detrimental to health"* – there is pretty much universal agreement on this.
- But a few questions emerge when we dig deeper:
    - High sugar intake can drive excess calorie intake and fat accumulation – which cause health issues.
        - First, many quacks lay every health issue at the feet of "sugar", in an absurd way.
        - Often, as a pushback to that, some can claim sugar is ONLY a problem in the context of a hypercaloric diet.
        - Now, indeed that is perhaps the primary issue
            - E.g., see Khan & Sievenpiper, 2016
- So **'sugar → hypercaloric diet → weight gain'** is one mechanism. However…
    - What about in situations of eucaloric or even hypocaloric diet?
    - In a situation where someone is not overconsuming calories or gaining weight, what health impacts on health are there?
    - And if there are these calorie-independent effects, at what thresholds do they occur?
- **What is "excess"?**
    - How much sugar counts as a 'high intake'?
    - Does this level differ based on other factors?
        - E.g. total calories, diet quality, insulin resistance of the individual?

Impact on Glucose Tolerance, Insulin Resistance, & Diabetes Risk

Moore & Fielding, 2016:

> *"The effects of specific sugars at usual intakes as part of an isoenergetic diet are less clear. The glycaemic response to food is complex and mediated by many factors, but sugar intake is not necessarily the major component."*

Lean & Te Morenga, 2016:

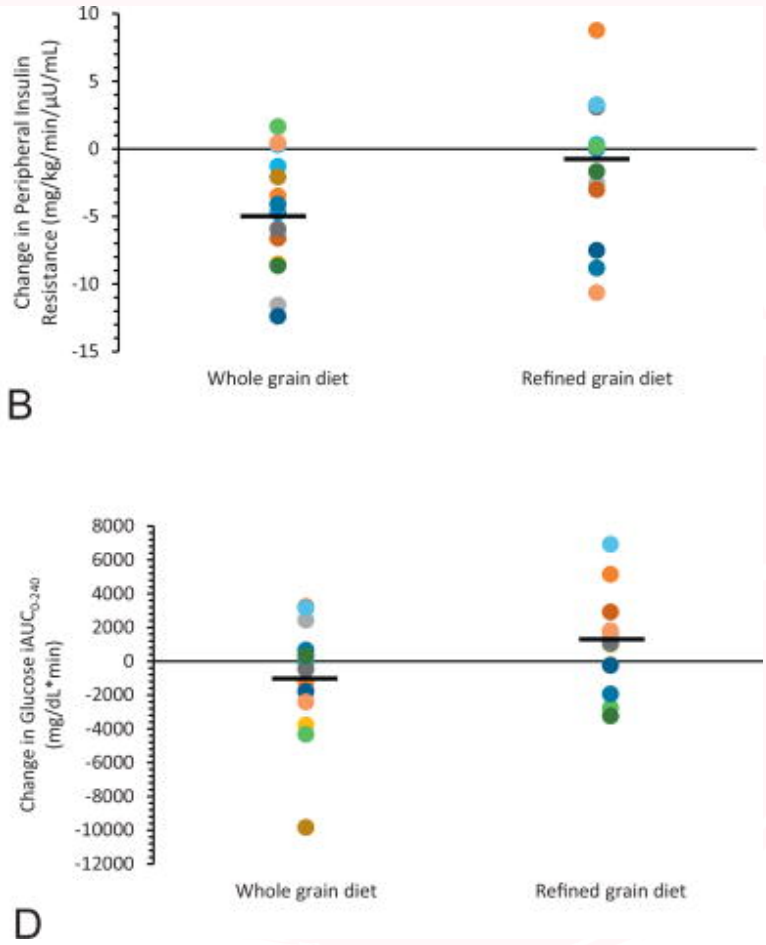
> *"Excess sugar can promote weight gain, thus T2DM, through extra calories, but has no unique diabetogenic effect at physiological levels."*

Whole Grains vs. Refined Grains: Impact on Glucose Tolerance

Study: Malin et al., 2018 - *A Whole-Grain Diet Reduces Peripheral Insulin Resistance and Improves Glucose Kinetics in Obese Adults: A Randomized-Controlled Trial*

- Study from John Kirwan's group
- Randomized, double-blind, controlled crossover trial
- Fourteen middle-aged, adults with obesity and at risk for diabetes
    - Any female participants were pre-menopausal and studied during the mid-follicular phase (i.e. 5–10 d post menses).
- Participants were provided either **whole-grain** or **refined-grain diets** for 8 weeks with an 8–10 week washout period between diets.
    - Blinding of subjects and investigators was achieved by packaging meals into identical containers so the visual appearance of the food was similar for whole-grain and the control, refined-grain diets
- The macronutrient composition of the diets was matched and consisted of **50 g per 1000 kcal of whole-grain or refined-grain**, respectively.
- All meals and fluids were provided throughout the study, and recipes were identical between diets, with only frozen ready meals and breakfast cereals differing in the source of carbohydrate (refined grain or whole grain).
- Dietary compliance was estimated by weekly food container weigh backs, and calculated as the percent difference between prescribed and actual caloric intake.
- There was **no difference** between whole-grain and refined-grain conditions for:
    - energy (2028±86 vs. 2016±83 kcal/d, P=0.84)
    - total carbohydrate (54.6±0.7 vs. 53.7±0.7%, P=0.45)
    - sugar (122±6 vs. 128±6 g/d, P=0.35)
    - fat (28.4±0.3 vs. 28.7±0.5%, P=0.63)
    - protein intake (18.1±0.3 vs. 17.5±0.3%, P=0.12).
- Diets differed by:
    - **whole-grain intake:** (90.5 ± 4.5 vs. 0 ± 0 g/d)
    - **dietary fiber intake:** (26.5 ± 1.4 vs. 20.1 ± 1.3 g/d)
- Both whole-grain and refined-grain interventions induced approximately 3–6% weight and fat loss
- Whole-grain and refined-grain intake improved fasting and postprandial **hepatic insulin resistance.**

- Whole-grain consumption reduced **peripheral insulin resistance** by approximately 18% compared with a 2% rise following refined-grain intake
- The intervention had no effect on **fasting glucose**, however, whole-grains lowered 2-hour glucose by approximately 2.2 mg/dl, although this did not reach statistical significance
- significant reductions in **glucose iAUC** of approximately 5% by whole-grains compared with a 23% rise following refined-grains
- **Fasting insulin** was reduced by both whole-grain and refined-grain diets.
    - However, **2-hour insulin levels** were reduced by 14% after whole-grain intake compared with a 39% rise with refined-grains



From: Malin et al., Metabolism. 2018 May; 82: 111–117.

So… whole-grain intake as part of a mixed-meal diet significantly improved postprandial glucose metabolism.

Whole grain may be better for glucose metabolism, but weight loss improved health outcomes in both.

NAFLD & Sugar (Leanne Hodson Study)

Study: Parry et al., 2020 - *Intrahepatic Fat and Postprandial Glycemia Increase After Consumption of a Diet Enriched in Saturated Fat Compared With Free Sugars*

- Participants were recruited from the Oxford BioBank
- Sixteen males
- All volunteers were free from metabolic disease, had a BMI between 25 and 30 kg/m2
- Randomized crossover design
    - Participants completed two 4-week dietary interventions separated by a 7-week washout period
    - Participants also followed a 1-week standardization diet, based on the U.K. Eatwell plate, prior to starting the respective dietary interventions
- The two dietary interventions were:
    - 1) a relatively **high-fat diet enriched in SFA** (referred to as SFA)
    - 2) a relatively **high-carbohydrate diet enriched with free sugars** (referred to as SUGAR).
- Participants completed 3-day diet diaries during all standardized and experimental diet periods
- Before beginning each dietary intervention, participants underwent a fasting study day, and upon completion of the intervention diet, participants underwent a postprandial study day that used stable-isotope tracers to investigate postprandial metabolism.

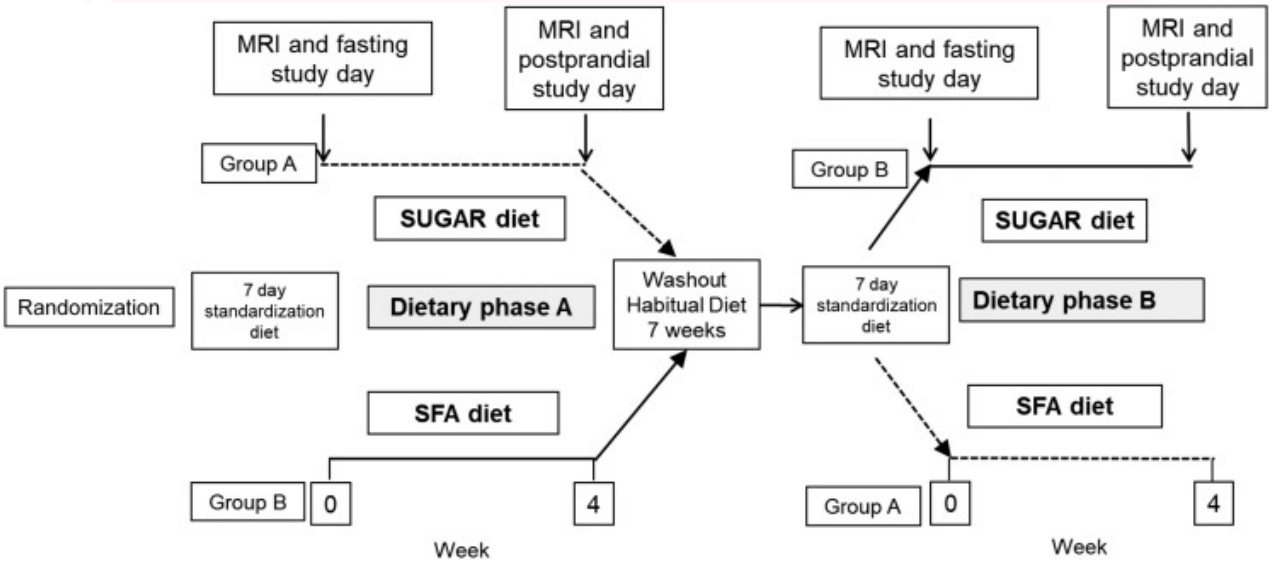


Image from: Parry et al., Diabetes Care. 2020 May;43(5):1134-1141.

- **The SUGAR diet**

    - Composition:
        - Fat = 20% total calories
        - Carbohydrate = 65%
        - Protein = 15%
    - ***20% of the calories were provided by free sugars*** added to the diet.
    - Participants were advised to adopt a low-fat, high–glycemic index diet and were supplied with candy and sugar-sweetened beverages providing ~**100 g free sugars daily**.
- **The SFA diet**
    - Composition:
        - Fat = 45% total calories
        - Carbohydrate = 40%
        - Protein = 15%
    - ***20% of the calories were provided by saturated fat (SFA)*** added to the diet.
    - On this diet, participants were advised to include red meat and meat products, full-fat dairy products, and typical fast food items (e.g., hamburgers, pizza etc.) and were provided with foods (such as cheese/all-butter biscuits and milk chocolate) that provided ~15 g SFA daily.
- The evening before the postprandial study day participants consumed deuterated water.
- Participants were fed a standardized test meal containing 40 g carbohydrate, 40 g fat, and 200 mg [U13C]palmitic acid to *trace* the fate of dietary FA.
    - See Premium episode: 'What Are Stable Isotopes? How Are Tracers Used in Nutrition Research?'
- Body weight, BMI, and waist circumference significantly increased after consumption of the SFA but not the SUGAR diet.

- Relevant to the particular **question/topic of this episode**, let's focus on the SUGAR diet…
    - Neither fasting plasma glucose nor insulin concentrations were altered in response to either dietary intervention.
    - Plasma total & non-HDL cholesterol *decreased* following the SUGAR diet.
    - **Liver fat (IHTAG):**
        - Significantly increased by 39.0 ± 10.0% following the SFA diet
        - **But unchanged in response to the SUGAR diet**

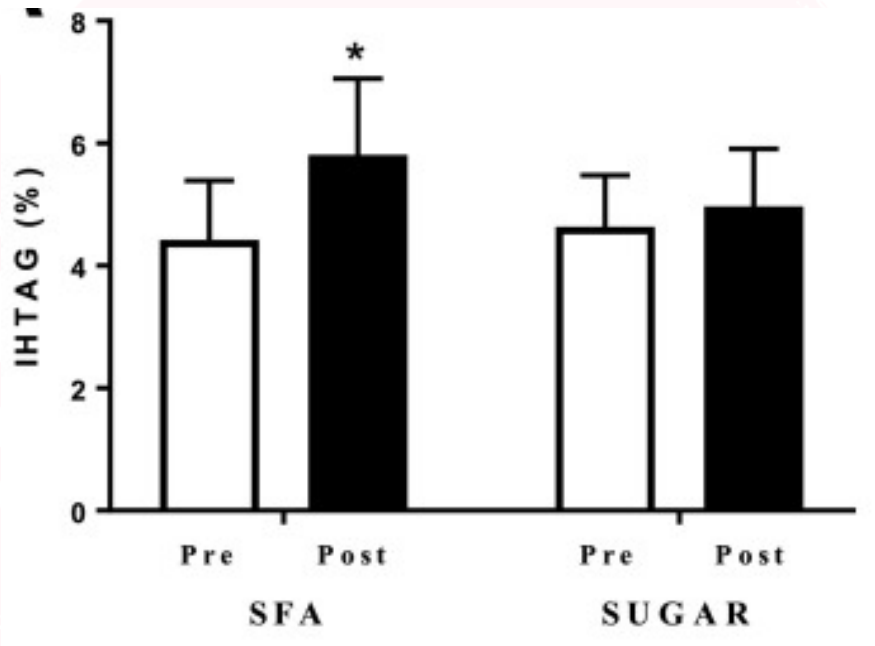


Image from: Parry et al., Diabetes Care. 2020 May;43(5):1134-1141.

- Linear regression indicated the increase in body weight observed after the SFA diet explained only 17.2% of the variance in IHTAG
    - This tells us that the increase in liver fat following SFA diet occurred *independently* of changes in body weight
- As a side note, when thinking about how diet impacts postprandial glucose responses, it was consumption of *the SFA diet* that resulted in exaggerated postprandial plasma glucose and insulin excursions, compared with consumption of the SUGAR diet.
- The negligible change in liver fat in response to the SUGAR diet is in line with results of others who have fed sugar-enriched eucaloric diets for 4–10 weeks. E.g.,:
    - Bravo et al., 2013
    - Johnson et al., 2013

Umpleby NAFLD Study

Study: Umpleby et al., 2016 - *NAFLD exacerbates the effect of dietary sugar on liver fat and development of an atherogenic lipoprotein phenotype*

- Participants:
  - Men aged 40-65y
  - BMI 25-30 with raised cardiometabolic risk, as assessed by a risk score used previously in the 'RISCK' study
  - Split in those with and without NAFLD:
    - Men with NAFLD (11)
    - Control (14)
- Two 12 week periods, crossover design, with 4 week washout
- **Diets:**
  - **high** in non-milk extrinsic sugars (**26% total energy**)
  - **low** in non-milk extrinsic sugars (**6% total energy**)
    - Note: The term NMES, as originally defined by the UK's Department of Health, includes free sugars added to food, but excludes sugar in whole fruit, and lactose, primarily from cows' milk
- Matched for macronutrient content
- There was no difference in reported energy or macronutrient intake between diets.
- Liver Fat Findings:
  - **Liver fat** was higher after the 'high-sugar' versus 'low-sugar' diet in both groups.
    - But men *with NAFLD* showed a relatively greater response than controls
- Body weight was higher after the high versus low sugar diets in NAFLD and Controls
  - At baseline:
    - NAFLD = 90.0 kg
    - Controls = 89.7 kg
  - After high-sugar diet:
    - NAFLD = 89.7
    - Controls = 88.9
  - After low-sugar diet:
    - NAFLD = 87.7 (2 kg lower than high-sugar phase)
    - Controls = 86.7 (2.2 kg lower than high-sugar phase)

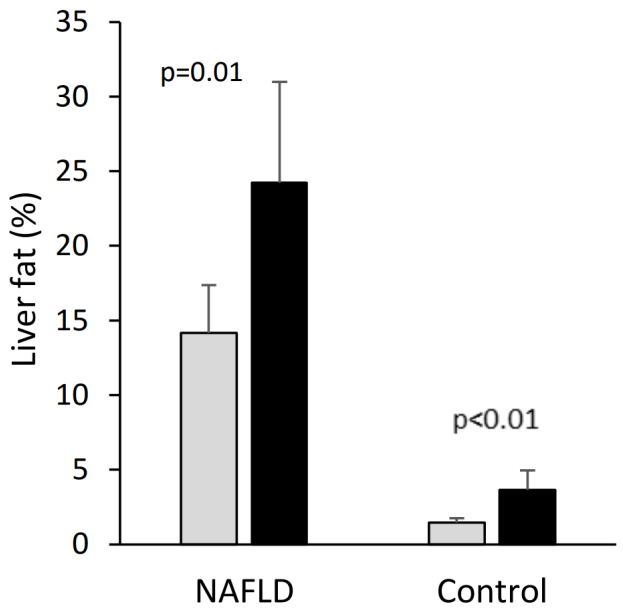


Image from: Umpleby et al., 2016, Diabetologia https://doi.org/10.17863/CAM.652

- **Lipoprotein** kinetics and the sources of fatty acids for triacylglycerol (TAG) production were measured using stable isotope tracers
- A high sugar intake increased **VLDL-TAG** production in both groups.

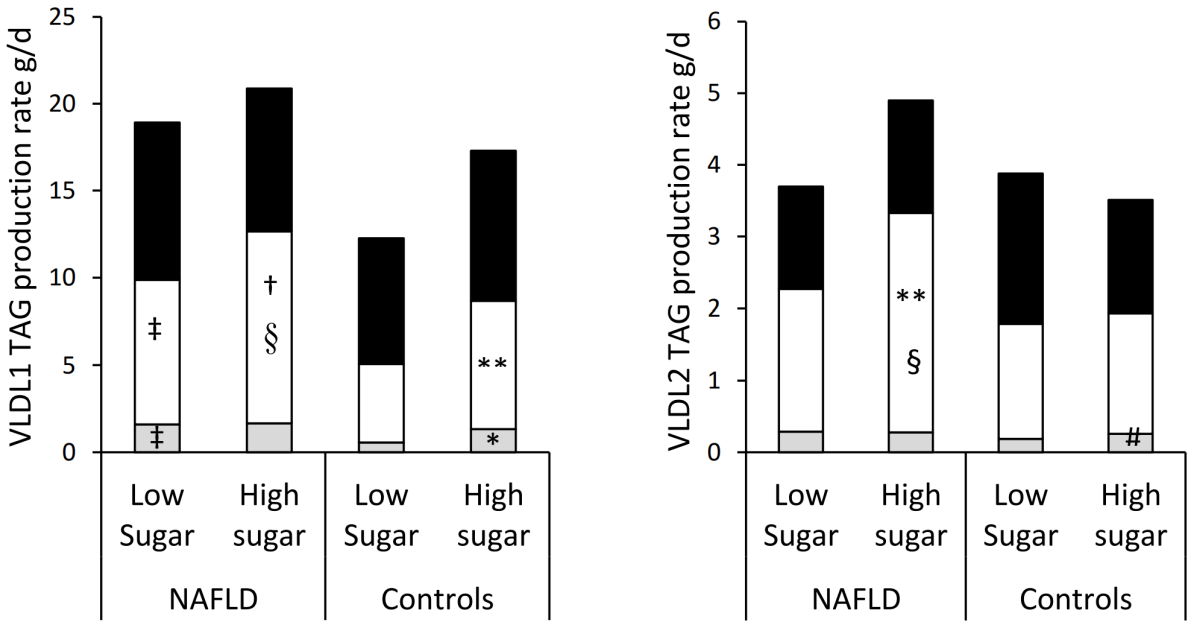
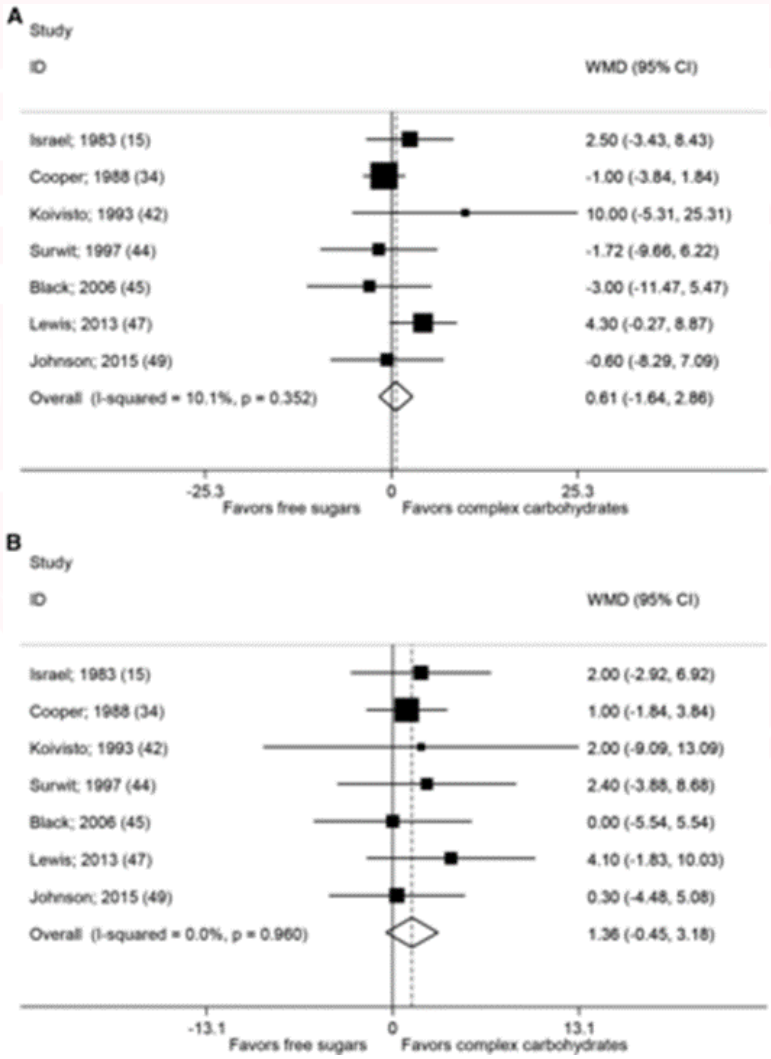


Image from: Umpleby et al., 2016, Diabetologia https://doi.org/10.17863/CAM.652

Fattore et al. – Effects on Blood Pressure and Lipids

Study: Fattore et al., 2017 - *Effects of free sugars on blood pressure and lipids: a systematic review and meta-analysis of nutritional isoenergetic intervention trials*

- Meta-analysis of intervention trials to compare diets that provide a given amount of energy from free sugars with a control diet that provides the same amount of energy from complex carbohydrates.
- 28 studies involving 510 volunteers were included.
- **Blood pressure:**
    - When free sugars were substituted for complex carbohydrates, no significant increases were detected in systolic or diastolic blood pressure



Systolic (A) and diastolic blood pressure (B)
Plot from: Fattore et al., Am J Clin Nutr. 2017 Jan;105(1):42-56.

- **Lipids:**
    - There were significant increases in HDL cholesterol, LDL cholesterol, and triglycerides.
    - However, for LDL cholesterol and triacylglycerols there was significant heterogeneity between studies and evidence of publication bias.
        - After adjustment for missing studies, these increases lost significance.
- Subgroup analyses showed that diets providing the largest total energy intake enhanced the effect of free sugars on total and LDL cholesterol and triglycerides.
- The increase of triglycerides was no longer significant when studies with the highest risk of bias were excluded or when only randomized trials were considered.

Kirwan RCT – Whole Grains & Blood Pressure

Study: Kirwan et al., 2016 - *A Whole-Grain Diet Reduces Cardiovascular Risk Factors in Overweight and Obese Adults: A Randomized Controlled Trial*

- Participants:
  - Thirty-three participants (6 men and 27 women)
  - Living with overweight or obesity
  - Aged < 50 years
  - No known history of CVD
- Randomized, controlled crossover trial
  - Two 8-week periods, with a 10-week washout between diets.
- **Diets:**
  - **Whole-grain**
    - Contained 50 g whole grains per 1000 kcal
    - Average = 93 g/d
    - Fiber = 29 g/d
    - Sugar = 130 g/d
  - **Refined-grain**
    - Contained 50 g refined grains per 1000 kcal
    - Average = 0 g/d pf whole grains
    - Fiber = 21 g/d
    - Sugar = 129 g/d
  - *Note:* Sugar intake was the same, so this is looking at the role of **refined vs whole grains**, rather than sugar per se.Participants were provided all of their food and fluids during both diet periods
- Calories and macronutrient composition was matched (except fiber)
- Blinding was achieved by covering whole-grain foods with sauce and by packaging meals into identical containers so that entrees appeared similar for both diets.
- Both diets achieved the same amount of weight loss – Around 2.5 kg decrease
- **Diastolic blood pressure:**
  - Decreased −5.8 mm Hg (95% CI: −7.7, −4.0 mm Hg) after the whole-grain diet
  - Decreased −1.6 mm Hg (95% CI: −4.4, 1.3 mm Hg) after the control diet
- Improvement in diastolic blood pressure was **> 3-fold greater** when they consumed a whole-grain compared with a refined-grain diet.
- So… we can consider these findings from two perspectives:
  - **One:** On a whole grain diet of the same kcal and macros, greater improvements

in blood pressure are achieved, compared to the refined grain diet.

- **Two:** Even on a refined grain diet, as the diet was hypocaloric and thus resulted in a 2.5kg weight loss, diastolic blood pressure decreased.

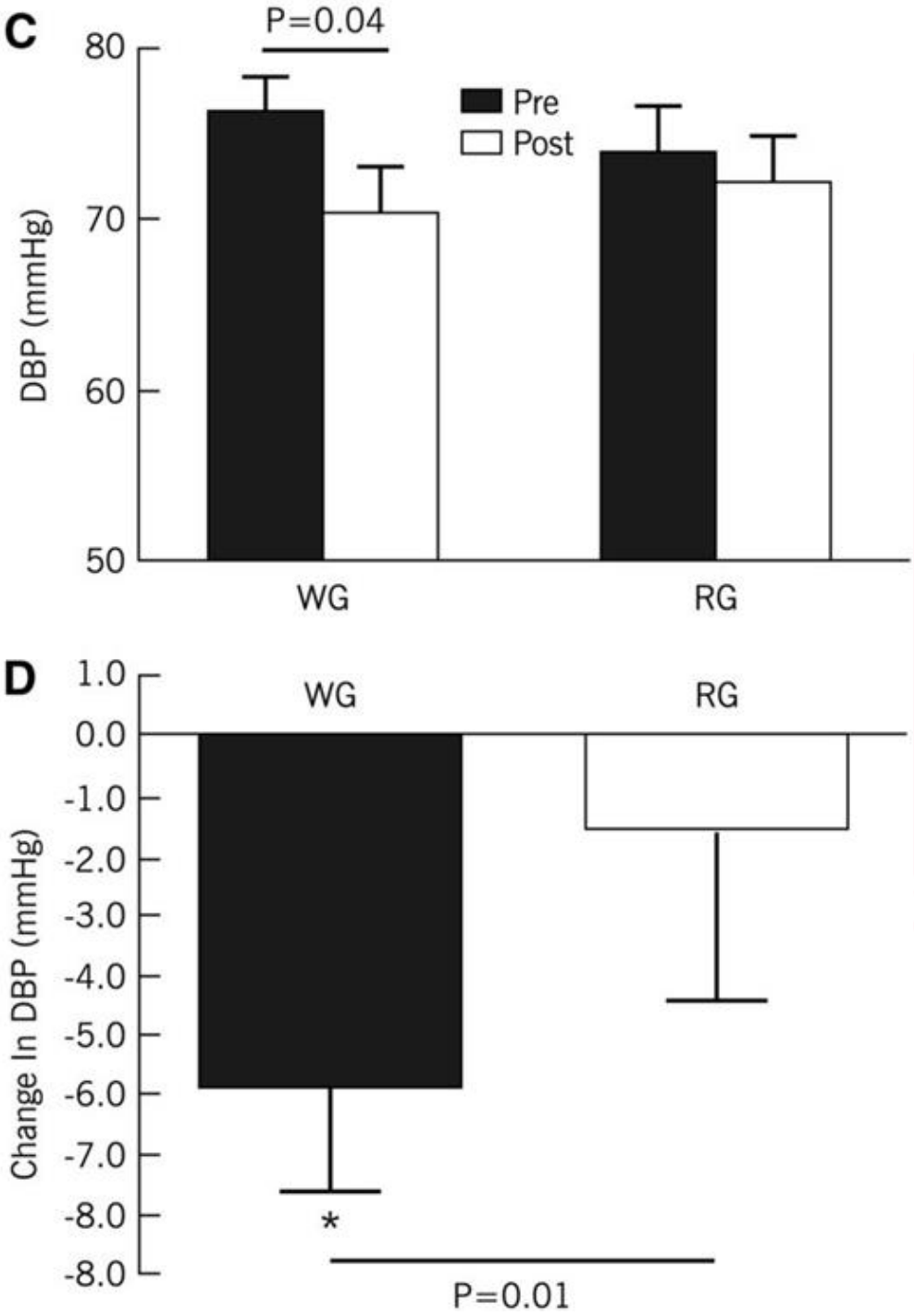
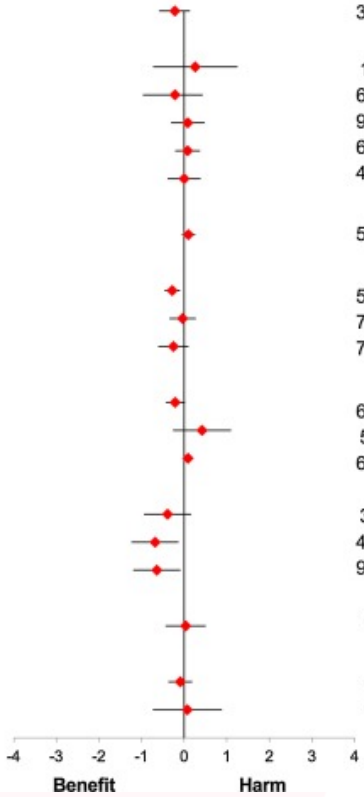


Image from: [Kirwan et al., Journal of Nutrition, Vol 146, Iss 11, Nov 2016, Pg 2244–2251]

Fructose

The meta-analyses are of isocaloric substitution trials, in which fructose was exchanged for other carbohydrate sources under energy-matched conditions:

Cardiometabolic endpoint		Comparisons	No.	Standardized Mean Difference (SMD) with 95% CI	I^2
Body weight [104]		31	637	-0.22 (-0.58, 0.13)	37%*
Fasting Lipids [106]	LDL-C	26	327	0.36 (-0.27, 0.50)	11%
	Apo-B	8	176	-0.21(-0.96, 0.43)	62%*
	Non-HDL-C	26	457	0.09 (-0.30, 0.47)	92%*
	TG	49	815	0.08 (-0.20, 0.36)	62%*
	HDL-C	27	525	0.00 (-0.38, 0.38)	49%*
Postprandial TG [111]		14	290	0.14 (-0.02, 0.30)	54%*
Glycemic control [109]	GBP	19	277	-0.28 (-0.45, -0.11)	56%*
	FBG	47	881	-0.04 (-0.34, 0.26)	78%*
	FBI	34	622	-0.25 (-0.60, 0.09)	70%*
Insulin sensitivity [109]	Whole body	16	265	-0.21 (-0.42, 0.01)	66%*
	Hepatic	3	25	0.42 (-0.25, 1.09)	51%
	HOMA-IR	39	806	0.09 (-0.03, 0.20)	66%*
Blood pressure [107]	SBP	13	352	-0.39 (-0.93, 0.16)	31%
	DBP	13	352	-0.68 (-1.23, -0.14)	47%*
	MAP	13	352	-0.64 (-1.19, -0.10)	97%*
Uric acid [108]		18	390	0.04 (-0.43, 0.50)	0%
NAFLD [112]	IHCL	4	95	-0.09 (-0.36, 0.18)	0%
	ALT	6	164	0.07 (-0.73, 0.87)	0%

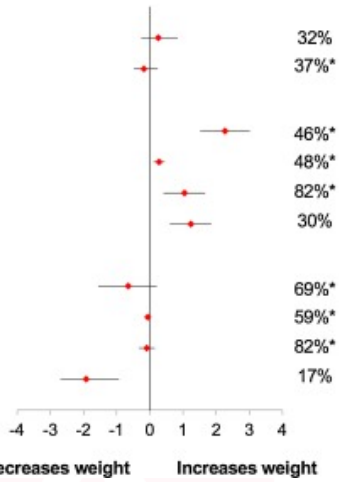


From: Khan & Sievenpiper, Eur J Nutr. 2016; 55(Suppl 2): 25–43.

Fructose-containing sugars and weight change in controlled dietary trials.

Forest plots of summary estimates from recent meta-analyses of the effect of different fructose-containing sugars interventions on indices of body weight:

Interventions	Sugar type	Comparisons	No.	Age group	Standardized mean difference (SMD) with 95% CI	I²
Sugars SUBSTITUTION						
Te Morenga et al. 2013 [46]	Sugars	13	144	Adults	0.26 (-0.26, 0.83)	32%
Sievenpiper et al. 2012 [104]	Fructose	31	637	Adults	-0.18 (-0.47, 0.23)	37%*
Sugars ADDITION						
Malik et al. 2013 [52]	SSBs	7	333	Adults	2.27 (1.53, 3.01)	46%*
Kaiser et al.. 2013 [137]	SSBs	7	565	Adults	0.28 (0.12, 0.44)	48%*
Te Morenga et al. 2013 [46]	Sugars	10	382	Adults	1.04 (0.42, 1.66)	82%*
Sievenpiper et al. 2012 [104]	Fructose	10	119	Adults	1.24 (0.61, 1.85)	30%
Sugars SUBTRACTION						
Malik et al. 2013 [52]	SSBs	5	2772	Children	0.65 (-0.20, 1.55)	69%*
Kaiser et al.. 2013 [137]	SSBs	8	3281	Both	0.06 (-0.01, 0.13)	59%*
Te Morenga et al. 2013 [46]	Sugars	5	1286	Children	0.09 (-0.14, 0.32)	82%*
Te Morenga et al. 2013 [46]	Sugars	5	2968	Adults	1.92 (0.94, 2.69)	17%



From: Khan & Sievenpiper, Eur J Nutr. 2016; 55(Suppl 2): 25–43.

Cocoa & Endothelial function Study

Study: Njike et al., 2011 – Effects of sugar-sweetened and sugar-free cocoa on endothelial function in overweight adults

- 44 adults (BMI 25-35 kg/m2)
- randomized, controlled, crossover trial
- Treatments were administered daily for 6 weeks, with a 4-week washout period.
- Treatments:
    - **sugar-free cocoa beverage**
    - **sugar-sweetened cocoa beverage**
    - **sugar-sweetened cocoa-free placebo**
- Cocoa ingestion improved EF measured as flow-mediated dilation (FMD) compared to placebo
- The magnitude of improvement in FMD after consumption of sugar-free versus sugar-sweetened cocoa was greater, but not significantly.
- *"Eliminating sugar from the cocoa product seems to amplify the beneficial effects of cocoa on endothelial function, although this difference was not significant perhaps due to the limited number of participants in the trial."*

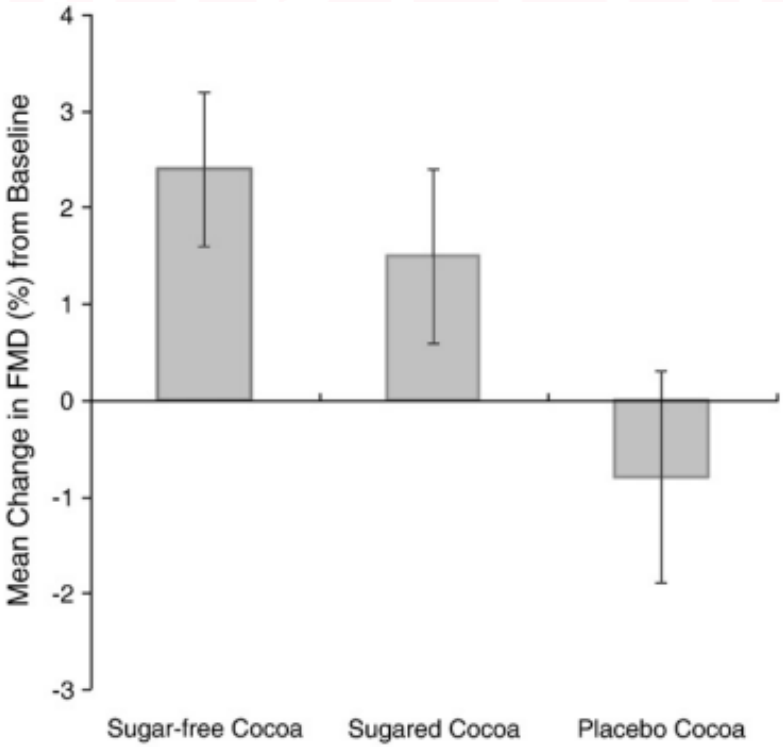


Image from: Njike et al., Int J Cardiol. 2011 May 19;149(1):83-8.

Conclusions

- Most general dietary guidelines recommend keeping added/free sugars to less than 10% of total daily calories. Some suggest that 5% should be the target for maximal risk reduction.
- The most recent data from both the National Health and Nutrition Examination Survey [NHANES] in the US, and National Diet and Nutrition Survey [NDNS] in the UK, shows average free sugar consumption in adults at 12.7% and 12.3%, respectively.
- The issue is what is displaced from the diet with a high intake of added sugars:
    - The more sugar in the diet, the more we have to displace other beneficial nutrients.
    - So if you consume more and more sugar-sweetened beverages for example, then to keep total calories in check, you will be displacing beneficial foods and overall diet patterns.
- In an analysis by Yang et al. (2014), 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.
- Most detrimental impacts of sugar tend to occur in the context of a calorie surplus, overfeeding, and weight gain.
- However, what is often missed by those who see no issue with added sugars on the basis of it only being an issue “only in hypercaloric diets”, is that in the real-world we don’t tend to control for calories. And higher sugar diets do tend to lead to hypercaloric diets.
- Exercise is a huge modifier of risk.