Episode Transcript

Danny Lennon: Hello and welcome to Sigma Nutrition Radio. You are listening to episode 468 of the podcast. My name is Danny Lennon, and beside me is Dr. Alan Flanagan. Alan, how are you today?

Alan Flanagan: I'm good. I'm wondering, given that expertise is dead, whether we should just drop the "doctor" and maybe drop any pretense to knowing what we're talking about whatsoever. Maybe people will like us more.

Danny Lennon: The good thing is that you've learned now is that your PhD in nutrition is now worthless. You're less credible to talk about nutrition now than if you hadn't done that.

Alan Flanagan: Exactly. If only I'd stuck with my blog in 2014 when I knew nothing.

Danny Lennon: Let's just lean heavily on your background in law and never mention any expertise in nutrition whatsoever. I think that would be good. Let's apply a legal lens to all these topics of metabolism.

Alan Flanagan: LDL has not been proven beyond all reasonable doubt and must be acquitted .

Danny Lennon: Yeah, let's just pepper in that language everywhere. That'd be excellent.

Alan Flanagan: Take a jury of our peers and present them the evidence.

Danny Lennon: If I can convince these people, then it doesn't matter what anything else is.

Today we have quite interesting topic and it's one I think probably has been many years since directly this has been looked at on the podcast and has came about from a couple of listeners who have found this an interesting question.

And so it is one that's worth diving into in a bit more detail. And we're going to be talking about the impact of sugar on health, which you can think: "oh, that isn't really that controversial or big of a question". But in the context of eucaloric or even hypocaloric diets.

So in other words, a lot of the time when we think about excess sugar being detrimental to health, I think this is almost universal agreement on this as a general statement, despite what background someone is coming at this question from. But there are a few questions that emerge when we dig a bit deeper.

High sugar intake can of course drive excess calorie consumption can then drive fat accumulation. And the combination of these causes a whole bunch of health issues out the backend. Now on, on one side we have. As we've discussed before, a lot of quacks will lay every single health issue at the feet of sugar and just no more context is provided and quite an absurd way.

And then I think often as perhaps a pushback to that, some can claim "look, sugar is only a problem to consider in the context of a hypercaloric diet". In other words, if you're in a calorie surplus or your sugar consumption causes a calorie excess, that's a problem. But if you don't over consume calories, then sugar intake is nothing to worry about and that is not a problem. And I think

there is some reason to maybe back that up. So I think there that comes from a decent place, but the question is: can we take that too far?

So what we're really trying to tackle today is in the context of there not being a calorie surplus, do we have reason to suspect sugar in itself is problematic? And if so, at what kind of threshold do we talk about here? What counts as a high intake that would cause problems? What type of problems do we see? And we're going to try and investigate some of that.

So given that preamble, we thought there would be a few key areas to focus this down on and to get into some of the key studies that really probably give us this best answer to that.

So first we're going to look at things around glucose tolerance in some resistance, diabetes risk as one kind of group. Then we'll look at non-alcoholic fatty liver. Then we'll look finally at some cardiovascular related outcomes. So things like blood pressure, maybe endothelial function or cardiovascular mortality more generally.

And I think within that, we should be able to get to some interesting answers for you. So maybe as a way to start off, if we think about glycemia insulin, diabetes risk, et cetera, this is one where people can presume that there's going to be a direct link. Before we discuss any specific studies, Alan, maybe could you open us up on the general background picture you think we have here of like just how much literature do we have that directly tackles this issue of high sugar intakes in the context of either a e caloric diet or a even a hypocaloric diet, in other words, no calorie access being present?

Alan Flanagan: Well surprisingly, there is a body of literature there but it's not as voluminous as one might think. And a lot of the available research that we have has typically been designed to really hone in on mechanisms. And there's nothing necessarily wrong with that per se but it is important to consider with experimental design what is it exactly that a study is seeking to achieve. And so a lot of the available literature on sugar or even specific monosaccharide types like fructose, has either focused on the effects of these sugars additional to the diet, i.e., It's consumed on top of an individual's normal ad libitum intake.

Some other experimental designs have been more deliberate in looking at, the effects of energy excess with a significant proportion of that from sugar. And the actual body of literature that exists that really looks at isocaloric conditions or in a controlled context and even looking at different types of sugars isn't as perhaps.

In terms of well controlled studies where we could really say that we could isolate the effects of sugar, there isn't necessarily as robust a total body of evidence depending on the outcome that we're talking about. So there is some of the studies that we'll discuss today are very good methodological quality, but we might be confined to a number of specific studies in that area.

And that again, is going to be relative to the main areas that we'll discuss. Glucose, intolerant states, diabetes fatty liver, and cardiovascular disease. Now for cardiovascular disease, there are slightly more of a body of evidence and there's been evidence, synthesis of controlled feeding studies in relation to blood pressure and also in relation to say, postprandial triglycerides or even fasting triglycerides.

So this is slightly more voluminous evidence based there, but yeah in relation to certain other topics for example the research on fatty liver, some of which we've covered before, a lot of the interventions that are quite interesting that have compared say fat to sugar have actually been in the context of overfeeding.

Although there is some very interesting research looking at. At sugar compared to both fat and then varying levels of sugar in, in control trials. There is a body of good quality evidence that we can perhaps use to come to some reasoned conclusions.

Danny Lennon: Yeah. So if we are starting with the topic of glycemia and whether there's different forms here where we can talk about the response to meals versus fasting glucose versus insulin resistance and so on, which will make clear as we go through different studies.

But from a general overview point, I think one interesting thing for people to know is that it seems almost intuitive for someone to think: "okay, if one diet has a high intake of sugar or more sugar than another, then surely that

means that someone's glycemic response in general over the course of a day is going to be worse".

And this again may be based on the idea of sugar has to cause more of a problem. But really this misses the general point that our glycemic response to meals generally, or certainly over the course of a whole day, is based on a whole range of factors, not just sugar as is sometimes painted online. And it's very simplistic to think that more sugar necessarily means that will be mean more of a glycemic response, independent of any other factor, whereas really it's complex in terms of how we have glycemic responses to foods, meals, and overall diet.

Alan Flanagan: Yeah, I think that's probably where a lot of this will get mixed up. So we've got, in terms of factors that can influence postprandial glycemia, and then related insulin responses, we can have the actual caloric size of the meal, the energy content of the meal itself. We can have the macronutrient content of the meal itself. And the reason that these will be relevant is because they'll impact on factors in the overall digestive process.

For example, the rate of gastric emptying will itself be a factor that then if that is a slower rate of gastric emptying that will influence a slower presentation of glucose into the bloodstream. We've also got the effects of for example the interrelationship between food in the stomach gastric responses, and then the secretion of incretin hormones like GLP- 1 which themselves have a role in attenuating postprandial glycemia. And then we've got the health status of the individual as well. So there's going to be differences in responses between people based on their levels of visceral fat or their overall metabolic risk and capacity.

And then of course, with any of these nutrient considerations, we've always gotta think about that bell curve of a nutrient from the kind of curve as it relates to risk. So there's going to be dose thresholds at which we might see in effect and not, and that's then going to be relevant. So there's going to be almost no way that for most nutrients we could ever say, or any nutrient that we could ever say in isolation, this is harmless.

And so then we get into questions of what's the actual level used in the study, what's the overall diet used? How is it isolated? The health status of the participants? And yeah and a range of these postprandial factors that will all

influence the magnitude of the glycemic response and then at concomitant the magnitude and extent of any required insulin responses.

Danny Lennon: And so maybe if we start looking to some of the literature that we've pinpointed that might be useful. And I think one of the things that maybe speaks to the maybe lack of direct comparisons, we'd ideally want; for example eucaloric conditions with differing levels of sugar, is that it's difficult to find lots of good quality trials that directly look at this.

So as maybe a first way in, one of the papers we've identified is one from John Kirwan's lab, Malin et al. 2018 study. And this doesn't actually address directly sugar per se as we'll probably mention later on when we look at the two different diets, but it more looks at whole grain versus refined grain intake within two diets in a randomized double-blind crossover trial. And so this might at least elucidate something about, is there an impact of whether someone is choosing whole grains versus refined grains on overall health, even without a caloric excess. So maybe to run through the basic setup of this study, this was an RCT done in 14 middle-aged adults with obesity and at risk for diabetes.

Any of the female participants, interestingly, were both premenopausal and studied at the mid-follicular phase, so they could of accounted for the time in the menstrual cycle, which is quite interesting. The participants were provided with their meals, so they were either given whole grain or refined grain diets for an eight week period, and then there was about eight to 10 week washout period between those. And then they would go over to the other diet. And there was blinding be able to done to these diets being, because they were packaged meals essentially. And through the use of like sauces and so on, it was blinded to the participants whether they were consuming a whole grain or a refined grain. Now the difference between those was the whole grain was 50 grams of whole grains for every 1000 calories within the diet.

The refined grain was 50 grams of refined grain per 1000 calories in the diet. So meaning that you have this difference of the whole grain diet on average ended up being about 90 grams or so of whole grains, whereas the refined grain diet had zero grams of whole grains per day. All of that was refined, and so you ended up seeing slight differences in fiber intake, which we'll probably come back to, but everything else was the same.

So energy intake was the same, all the other macronutrients were the same within the diet. The only thing different here is whether we have whole grains orrefined grains, and I think what is the reason we bring up this particular paper is that in both of these diets, you saw weight loss and fat loss occur.

Both diets ended up giving about the same amount of weight loss. And so this controls for that factor of our initial question of, okay, what happens if someone is not over consuming? In fact, if they're on a diet and they're losing weight, which we know promotes health in many different cases, what would happen if we have different levels of intake?

Now again, this isn't directly looking at sugar per se, this is more a comparison of whole grain versus refine grain, but it's something that kind of gets us at least towards that question for now. So with some of that context Alan, can you maybe talk about some of the results from that study that you think were most notable that kind of informed the conversation we're having today?

Alan Flanagan: Yeah, so as you said, diets were controlled there's probably three studies from John Kirwan's group that we're going to discuss today. And they'll all have the same setup that Danny just described. And they were really nicely executed studies again for free living nutrition interventions, the most that you can ask of a research group is that they prepare and provide the meals to participants.

The data on compliance suggests that there is around 90% compliance. And that was based on returned meals to the research team from the participants, and that was around 90% for both diets. So really excellent compliance overall over the eight weeks of the intervention and importantly in interpreting some of these metabolic outcomes, there were no differences in weight loss between the two groups.

There's no significant differences in weight loss over the eight weeks of the study. So the context of the findings that we're going to discuss now is really occurring in terms of differences slightly independent to a degree of weight loss differences, but of course, it's not necessarily going to be independent of weight loss per se.

So the magnitude of the difference is influenced potentially by by the difference between the diets. Although weight loss would have a role. And the main kind of finding that they emphasized was the effect on insulin resistance, peripheral insulin resistance and this is reported in the paper as an 18% decrease in insulin resistance in the whole grain diet group. So that's comparing there before and after. And around a 2% increase following the refined grain intake diet. Now the plots they have in the study also have the individual plots of the participant's data and so overall, for example, with peripheral insulin sensitivity we can actually see that really in terms of increased insulin resistance, that seems to have been driven by some fairly big changes in two participants. Whereas the rest of the participants in the refined great diet group, whereas the refined grained diet group the majority of the participants are still indicating some decrease in peripheral insulin resistance.

It's just not to the same magnitude as the whole grain diet. I thought that was an interesting finding in this study because when we look at both total carbohydrate and sugar intake, total carbohydrate intake was pretty much the same; 54% of daily energy intake and total sugars were 122 and 128 grams in the whole grain and refined grain groups respectively.

So they're well-matched for these dietary factors. And yet we're seeing a kind of potentially additive effect on of the whole grains. And I think that phrasing is important because although there is clearly some participants who do have a deterioration in peripheral insulin resistance on the refined grain diet, we can still see that most of the participants had some degree of improvement even on the refined grain diet.

So although these between group differences would lead, to a conclusion potentially that whole grains are incredibly superior this isn't necessarily a damning knock on refined cranes necessarily entirely. And then I think other than the peripheral insulin resistance to discuss is the glucose incremental area under the curve, incremental area under the curve is basically a calculation that really tries to encompass the total postprandial period above, over and above a, whatever the fasting measure of glucose in the participants wear and that decreased by about 5% in the whole grain group. And it actually increased by about 23% in the refined grain group.

So overall, there was this 2.2 milligram per deciliter, lower two hour glucose levels. And so there was a difference in these postprandial glucose parameters. And again, that is borne out in the data. We can see that, yes, there were a couple of individual participants in the whole grain diet that had slightly higher blood glucose change in blood glucose, incremental area under the curve mostly the whole grain diet was towards a reduction in that postprandial or post-meal glucose response. Whereas in the refined grain diet actually we could see more participants. Were looking at elevation in their postprandial glucose. So we are seeing an effect that is not necessarily related to sugar per se, because sugar and total carbohydrates, but it is related potentially to some of the property differences between whole grains and refined grains.

Danny Lennon: Yeah. So to reiterate some of that context, because that really is important, what you finished on there of, in this study, sugar intake was essentially the same. All of their macronutrients were the same. So what we're really getting at here is more about the question of in the context of where we don't have an over consumption of calories, macronutrients are the same and we just have maybe one change like this of whole grains versus refined grains, does that change in food quality, for lack of a better term, have an impact here. Specifically if there's refined grains. Because when we're talking about the sugar question, this might be something that people turn to, right? I don't need to bother with these certain whole grains. As long as there's not this calorie surplus present, having refined grains or maybe sugar in other context won't cause problems.

Now here again the devil is in the detail as you say, that there are some cases where there's no real difference. There are some cases where there's difference between the groups, but by and large, there's still benefit for both groups, probably due to the weight loss that was incurred. And then whether is some degree of a detrimental impact seems to be on this postprandial response to things like insulin and possibly glucose for the refined grain group.

So that leaves us to conclude that, yeah, ideally you could probably say that more whole grains versus just refined grains would have some degree of health benefit. But in this context where we have a hypocaloric diet, we couldn't really say just by having the refined grains that led to a major degradation of one's health in some sort of damning way.

There were these negative changes in postprandial response, but by and large it wasn't this complete degradation. So it, all those things together need to be taken in to some degree of context. So I think that's a useful starting point.

Alan Flanagan: Just to say that when they did their correlation analysis to look at which came first, chicken or egg, the decrease in peripheral insulin resistance was the strongest correlation was with the reduction in two our postprandial glucose levels. And again, that is relatively consistent with what we would expect, but it is just to note that perhaps even, yeah, in the context of an isocaloric diet, the idea that we can just dismiss considerations of food quality because of the varying properties that whole grains, for example, may have, I think is possibly a little shortsighted, even though, yes if we were focused only entirely on weight loss and "hashtag calorie deficit", then this study would also support that. But that's probably just missing a bit of the point. Yeah.

Danny Lennon: One other thing I find interesting about this, and that wasn't really the point of this particular study, but for the question that we have, is that when you look at the sugar intake in these two diets, as you said, they're both pretty much in around the same, but they're between 122 and 128 grams per day.

Which when you look at that in the context of these diets, we're around 2000 calories per day as a percentage. That's actually pretty high. It's probably above what we would ideally see again, depending on where those sugars are coming from, because, as we'll probably clarify later, we'll mainly be talking about the limits on sugar intake in the context of added or free sugars as total sugar, but we will come back to that. But it's still worth noting that there is certainly not very low sugar intakes we're seeing in either diet here.

So maybe to continue on with this and you've mentioned that there are other studies from this group that we wanted to look at. There was one the following year, 2019 from the same group I believe the same lead author, Malin. Do you want to maybe bring us through what aspects of that second study you think are worth highlight?

Alan Flanagan: Yeah, so we won't go over too much the design because it's the same design as the previous one. So it was 50 grams per whole, per 1000 calories of whole grains versus 50 grams per 1000 calories of refined grains.

Again, all meals prepared eight weeks of the intervention, 13 participants in total. And this was also hypocaloric, and there was no difference in weight loss in between either diet. But the main goal of this study was to look at what's known as glucose stimulated insulin secretion, a measure of the responsiveness to the ingestion of glucose.

And that was increased significantly on the whole grain diet compared to baseline. But actually, again, there was no significant difference between groups. And when we looked at, say, two hour insulin levels in this study, that was lower on the whole grain diet compared to the refined grain diet. But again, these kind of between group differences were not statistically significant.

Now again, we don't want to fall for p-value idolatry; ultimately if we looked at the outcomes, the whole grain diet did lead to a result in terms of postprandial markers that were measured tended to decrease most of them. Whereas the refined grain diet, the trend was for increases in some of these, for example, postprandial insulin or postprandial glucose.

Overall, this suggests that there's perhaps, and there's some mechanistic explanation for why this would be, but that the whole grains are exerting some effect on insulin secretion, and it may be mediated by en cretin hormones, although that wasn't suggested in the present study. That comes from other research that has looked at this kind of increase in things like GLP-1 and GLP that support an insulin response.

So yeah, I think this was again, an interesting study limited by its small sample size, well conducted and controlled overall, suggesting that whole grains have a beneficial stimulatory effect on insulin secretion and concomitant reductions in postprandial glucose compared to refined grains. But again the magnitude of much of the difference could have been washed out a little bit by the fact that this was that there was, relatively modest weight loss. Nevertheless, it was weight loss and we would expect that to have a bearing on the outcomes.

Danny Lennon: So far, certainly nothing that we can make definitive conclusions on, particularly if we're talking about sugar, which as we've mentioned, wasn't direct source of some of these trials. So when we look at the evidence around sugar, it's difficult to find the types of studies we've just mentioned that were in the context of the whole grain versus refined grain diets, or at least that I'm aware of, that have done a similar type of well designed trial, specifically on the question we're asking, but certainly there's a way to piece that together, and we might not go through all of that, but as a couple of the review papers that we're going to highlight for people listening that are certainly worth reading they can allude to maybe some of the conclusions we can come to on this particular outcome before we move on.

One that is worth highlighting is paper from Bernadette Moore and Barbara Fielding 2016 paper. This was a kind of a review opinion piece where they were looking at this question and whilst noting that there's definitely detrimental impacts of excess sugar intake, particularly as we've already outlined, it tends to be in the context of hypercaloric diets. They say: *"...the effect of specific sugars at usual intakes as part of an iso energetic diet are less clear. The glycemic response to food is complex and mediated by many factors, but sugar intake is not necessarily the major component"*. Which something we touched on at the outset of the podcast.

In other work that is more related to type two diabetes, Mike Lean, who we've probably referenced on the podcast before, was one of the authors along with Te Morenga, of a opinion piece that appeared in 2016 where they said: *"excess sugar can promote weight gain, thus type two diabetes through extra calories, but has no unique diabetogenic effect at physiological levels."*

And so based on some of the reviews in this area, that kind of lends us towards this few of, again maybe there is a question here of without that excess of energy, is there actually a problem from these high sugar intakes directly? Based on some of those conclusions and maybe your reading of in this area more broadly, beyond the couple of studies you mentioned so far, what other elements should we touch on in relation to any of the glycemic diabetes related outcomes when it comes to this question of sugar without calorie excess?

Alan Flanagan: I think looking at this, it is difficult. That there are some, context we can give this. When we discuss cardiovascular risk factors and we

discuss, for example, triglycerides, we know that there is potentially an interaction between triglycerides and then, metabolic health from the perspective of say, insulin resistance in the liver, peripheral insulin resistance, but, again, every needle that we have on this body of evidence points in the direction of this occurring in the context of either sugar, overfeeding, or sugar contributing a significant proportion of total daily energy in the context of surplus energy or hypercaloric conditions.

And so when it comes to isocaloric conditions, it does appear that many of the proposed deleterious effects of sugar, per se fall away as it relates to postprandial, glycemia or insulin. And the Malin and colleagues studies that we discussed there really highlight that, what we saw was relative improvements overall.

In most parameters as of results, likely of weight loss, but potentially some greater effects of the whole grain. That did occur in the context of a very high sugar intake. In both diets, it was between 15 and 20% of total energy and closer to 20% if the numbers in my head are correct.

So I think from the perspective of postprandial glycemia again, it would be difficult to argue that there is a particularly deleterious effect of sugar and then compared to whole grains, refined grains, maybe less of a positive for some of those outcomes. But I think it's difficult based on the totality of limited experimental research that has looked at this to find a uniquely negative impact of sugars on either postprandial insulin or glucose responses.

Danny Lennon: And like you say, some of that will be given more context when we look at some of the other outcomes, particularly in relation to cardiovascular disease a bit later on. But to move on to the second outcome that we wanted to talk about, which is non-alcoholic fatty liver disease and the accumulation of hepatic fat in particular, which may be particularly deleterious.

There's some interesting work in this area, some of which gets into the big question around fructose, which often comes up in this area or different types of sugars, but maybe as a good place to start, one of the really interesting and informative studies comes from Parry and colleagues 2020. This is from Leanne Hodson's group, who I think you've mentioned on the

podcast a number of times is one of the stars of NAFLD research. And so in this study, this was participants from the Oxford Biobank, 16 male participants. All of them were free of metabolic disease and had a BMI between 25 and 30, meaning they were in that BMI classification of overweight but not obesity.

And this was a randomized crossover design. So participants completed two four-week dietary interventions. In between there was a seven week washout period and then switching over to the opposite diet intervention. Now, one of the things they also had was this one week standardization diet running into the start of each diet.

So one week based on the UK EatWell Plate which is the general dietary recommendations, and that was done before each intervention to standardize that going in the two diet interventions end that we're comparing is one that's a high saturated fat diet. So this was high fat diet, enriched with saturated fat, and then they had a high sugar diet. So this was high carbohydrates enriched with more free sugars. So they completed each of these diets. There was diet diaries collected during the experimental period, and they also had a fasting day that they completed beginning. Each dietary intervention were able to collect more data, including the use of stable isotope tracers.

And then we have this comparison between what happened to things like intra hepatic triglyceride. So that those triglycerides in around the liver on the sugar diet and then the saturated fat diet and what we're going to see. So again, this is a particularly useful study because there's a lot of work done in this area comparing sugar and saturated fat.

But a lot of those are overfeeding studies where we see this really clear body of evidence. You've touched on that in previous episodes. This one doesn't have an overfeeding element, but just has high free sugars or high saturated fat that are enriched in them. So by that we have them, the free sugars content of the sugar diet here was 20% of total energy.

The saturated fat diet was 20% of total energy from saturated fat specifically. And then we're able to compare them to see if there's differe. Even when we're controlling for overall calories, controlling for protein and people not gaining weight. So with that, let's start walking through some of the results

here. What are the most notable and the most important for the question we're trying to get to

Alan Flanagan: today? Yeah, so I think the first off is that although this was a eucaloric intervention, i.e., the energy balance was maintained was sought to be maintained in both diet groups and both were going to be at that maintenance level of energy.

There was an increase in body weight of about one and a half kilograms during the saturated fat, the high saturated fat diet. And this is important to deal with at the outset because people that would be of the "sugar is to blame" camp will push back on the fact that there was weight gain.

Now that was likely explained by an extra 300 calories per day in self-reported energy intake during the saturated fat diet. Possibly an argument against it's all satiating if you eat a high fat diet because there was some passive over consumption, but nevertheless, importantly, from a methodological standpoint, the the increase in body weight was addressed relative to the increase in intra hepatic triglycerides using a regression analysis to see which was more predictive.

And so what was observed with this was a body weight increase of one and a half kilos in the saturated fat diet compared to only 0.2 kilograms on the sugar diet. But liver fat intra hepatic triglycerides increased by 39% on the saturated fat diet, and it didn't change. So there was no change in response to the sugar diet.

So the question then is how much of that increase in liver fat was driven by the increase in body weight? And the answer to that based on the regression analysis is around 17% of the increase in liver fat was explained by the increase in body weight i.e the vast majority of the increase in hepatic fat was explained by the saturated fat content of the diet.

So this is congruent with what we've seen in other lines of evidence, both in overfeeding and under and energy balance that saturated fats have a particularly potent effect on increasing liver fat, and that's independent of body weight, however, coming back to the vilified sugar.

In this study, actually what we could see is really no effect on body weight and no effect on liver fat absent overfeeding. Now, this is in contrast to other research both from this group and others that has looked at sugar in the context of overfeeding. And we do see a significant increase in parameters that are relevant for liver fat and for even diabetes risk.

So de novo lipogenesis the synthesis of new fat from non-fat sources. New triglyceride can be increased in response to sugar overfeeding, but what happens is those parameters that we typically see increase in response to sugar, when it's consumed in the context of overfeeding, really fell away in this study where there was no excess of energy and the diet was isocaloric.

And this extended to postprandial metabolism measures glucose and insulin were greater and were elevated for a more prolonged period in response to saturated fat compared to sugar. There was an increase in postprandial free fatty acids or non-esterified fatty acids in response to sugar. But there was actually no change or difference between the diets in de novo lipogenesis either.

So overall, this really did not show any particularly deleterious effects of sugar on liver fat itself, on body weight or on the metabolic parameters in the context of an isocaloric feeding of 20% of the diet from free sugars or added sugars.

Danny Lennon: Fantastic. And as to really emphasize that, whilst you noted in the saturated fat group there was this slight increase in body weight, there was also an accounting of that in the linear regression.But nevertheless, for the question we're talking about today, we even don't need to think about that. We can focus in on this sugar group and realize that, as you've said, we have a diet of. 20% added sugars to the diet. We have participants that were advised to eat a high glycemic index diet. They had about a hundred grams of free sugars per day.

It was supplied with candy, sugar sweetened beverages, et cetera. So all the things that we shouldn't be doing, but in this context of a lack of overfeeding, we see that there was no change in. Fasting glucose insulin concentrations. We see that there was a decrease in things like non-HDL cholesterol, which we may come back to.

And then the most importantly for this study, the liver fat was unchanged in response to this level of sugar intake. And as you noted, where we see this deleterious effect of sugar in the context of liver fat accumulation is in overfeeding studies. And in fact that the authors noted a couple of other studies where there's sugar enriched eucaloric diets. One is a study by Bravo and colleagues. One is by Richard Johnson's group 2013 study. Where again, in those situations, either high fructose or high glucose diets didn't lead to changes in liver fat, when we have this eucaloric diet in place. And so at least for non-alcoholic fatty liver disease or fatty liver accumulation based on this study, there doesn't seem to be that impact.

Now, another really good study to maybe add to that and to talk about a bit more detail that I think was really cool is one that you'll definitely be very familiar with from Umpleby and colleagues 2016 cause of the, of course this is primarily from the team at the University of Surrey including Bruce Griffin and others who are well within your circle. And so this is a study you no doubt know.

This is quite cool, you have a similar demographic here of middle-aged BMI in that overweight, so 25 to 30 BMI. In this context, it was a raised cardiometabolic risk and you had here a control group and then also a group that had non-alcoholic fatty liver disease.

And so this is a cool study to see what is the impact of already having naled and does that impact things? So this was two 12 week periods, crossover design, foric washout, and they're comparing high added sugar diet and one that is low. So by high and low here they noted that it was 26% of total energy from these non milk extrinsic sugars and the low group was 6% of total energy from non milk extrinsic sugars, which would be pretty much close to the recommendations that we'll probably talk about later on. Now for those of you unfamiliar with this term 'non milk extrinsic sugars', this is just a term used originally by the UK's Department of Health. And so it includes free sugars added to food, but excludes sugar in things like whole fruit. And then also a sugar like lactose, which we would get from milk, hence the name non milk extrinsic sugars.

So now we have these two diets matched for things. For this added sugar content. All the other macronutrients were the same. We have 26% of total energy from these free sugars versus 6% in the low diet. And then they looked

at whole bunch of really cool things, again, using stable isotope tracers lipoprotein, kinetic, and then some of the impacts in both the group with non-alcoholic fatty liver disease, and then the control; did not have fatty liver. And then there's a whole bunch of things that we can maybe walk through.

So what are the first things that jump out with you and if there's any extra context that I haven't touched on here, Alan, that you can maybe illuminate people on, because I know you're very familiar with the, this study and have talked to the authors about it. Can you maybe add in and fill a few gaps that might round out our understanding of this?

Alan Flanagan: No I think that's largely it, except for the distinction between VLDL-1 and VLDL-2 because that's going to be particularly important for interpreting and considering the findings. And I think this is probably something we've discussed before on previous podcasts related to lipids or cardiovascular disease.

But we've touched, I know we've definitely touched before on the fact that for lipoproteins to, to be atherogenic, yes they need to express ApoB but then their particle diameter size is also relevant. And typically very large particles like chylomicrons, which absorb fat when we have digested a meal of the fat coming in from that meal, are really just too large to actually penetrate the arteries.

And this is also the case for VLDL in terms of larger VLDL. So that would be VDL one in this context, whereas VLDL-2. Is a smaller and therefore more atherogenic form of VLDL. And at the start we also touched on the fact that yes, we've got these various gastrointestinal processes that can all relate to postprandial metabolism, but we also mentioned that the health status of the host, of the participants or of the individuals is going to be a moderating factor.

And that's precisely what this study showed, which was really interesting. So the participants with NALED had overall a higher total increase in VLDL, triglycerides from both diets. Okay? So whether they were consuming the high or low sugar diet, The fact that they already had fatty liver meant that they were particularly susceptible to even lower levels of sugar in the diet in terms of overall the LDL increases in the LDL triglyceride.

But what was then interesting if we started to look more specifically at the effects of the diets themselves, was that in the controls who had just low normal levels of liver fat, their increase in total VLDL primarily was evident in the form of VLDL-1. And then for participants with NAFLD, it was primarily in response to high sugar VLDL-2.

So from the high sugar diet, 26% of total energy from added sugars or free non milk extrinsic sugars. People with normal liver fat, low liver fat controls, and people with NAFLD are having a completely different metabolic response in terms of the profile of their lipoprotein response to sugar.

And this may be because with the participants with nael with fatty liver there was a greater contribution to new VLDL synthesis coming from visceral fat. And interestingly, de novo lipogenesis, which again is typically the focus people hone in on when it comes to sugar. They're like sugar increases the synthesis of new fat. That's de novo lipogenesis.

This was only between four to 8% of a contribution because they did stabilize atop analyses. They were able to precisely trace the metabolic fate of the of the kind of substrates in the body. And to trace the origin of the triglyceride carried in VLDL and de novo Lipogenesis only contributed four to 8% in both groups on either the high or low sugar diet.

So both men with fatty liver and men without fatty liver, and on either the high or low sugar diet. So this is suggesting that in, again, in the context of an isocaloric condition where energy is not being over consumed, the synthesis of new fat from sugar de novo Lipogenesis is not contributing substantially to any increase in triglycerides and in VLDL.

But in fact there is a modifying effect of the host in response to sugar such that men already with fatty liver in this context, essentially presented with a more atherogenic profile particularly in response to the high sugar intake. And so this is likely to be an explanation for why there are certain strata in the population consuming.

This was in the study designed to reflect the 97th percentile and the lower 2.5 percentile of UK dietary intake. So there are likely subsets of the population that are potentially more vulnerable to the cardiometabolic consequences of

a high sugar intake as it relates to increased VLDL-2 synthesis from that high of sugar.

Danny Lennon: Yeah, so a couple of really interesting things there. First, we see this differential response between those with preexisting non-alcoholic fatty liver disease versus the controls in terms of the, their response to these different diets and the accumulation of both the liver fat, but then also this VLDL production and those differences that you noted there.

One of the other aspects to this, that when people dig in to look at some of the changes that whilst we could note there's this differential response in general for both groups between the high versus the low sugar, when you look at the body weight changes from baseline to after the sugar diet, their body weight seems to be pretty much around the same.

Whereas after the sugar diet phase for each of the groups, that both of them are about two kilos lower than after say the high sugar phase or indeed at baseline. And so here we have to account for this again, of when we're seeing, even though there is a slight difference here with the sugar in the context of the low sugar diet that is coming alongside this two kilos of presumed weight loss, or at least based on the reported body weights that were in some of these tables here, if I'm reading this correctly.

Alan Flanagan: Yeah. And I think that's again, potentially a reflection of the sugar levels similar to the comment we made in relation to the Parry and colleagues study on fat. And the relevance of this potentially is for considering external valid validity or generalizability where there is the potential for higher intakes or lower intakes of particular nutrients to perhaps better facilitate in a free living context energy increases or decreases. So I think it is something to consider.

But again, ultimately the most kind of interesting finding was the differential response of the VLDL subclasses and how that was and that was. Tho those analyses were adjusted for body weight. Yeah.

Danny Lennon: So that very intriguing finding and we will come back to the pragmatic point you raised about what happened in free living context, which is oftentimes maybe left out of these discussions of sugar not being problematic.

Let's maybe round off the fatty liver stuff with the final paper is one you earmarked the Johnston and colleagues 2013 paper where we have particularly hones in on the question around fructose. Can you maybe give an overview of why this is a particular useful paper to look at?

Alan Flanagan: Yeah. I think because fructose as a monosaccharide, as an isolated single sugar has really been a big focus of a lot of the sugar research generally. And many of these studies and a lot of the wider research, sugar as a word, which could mean any number of types of sugar is often essentially just a proxy for fructose. And fructose is most commonly used in a lot of these interventions. There's also some interesting metabolic pathways that fructose is involved in that are relatively unique and that are suggested to explain certain deleterious effects of fructose, particularly on triglycerides upregulation and synthesis.

And suggested to then contribute to liver fat. And so the problem prior to this study was that much of the research in terms of available interventions had not been controlled and was consuming excess sugar or fructose in the context of a ad libitum background diet. So participants were eating whatever they wanted.

There was one study which was interesting but still does the rounds as Merckin colleagues in 2012. And participants just ate their normal background diet. There was no energy control on that diet. And then they consumed a liter of Coke Day, a liter of diet Coke, a liter of milk and a liter of water.

And of course you could see this big blow up in visceral fat. And in that study and other deleterious effects, and again, everyone honed and you didn't see that on the Diet Coke, and you actually saw some benefits from drinking a liter of milk a day. And there was no change on water.

But, so studies like that really generated a lot of this focus on fructose or on high fructose corn syrup, but they weren't very well controlled. So this study; under controlled conditions compared 25% of energy from fructose and 25% of energy from glucose in a controlled background diet that contained 55% carbohydrate, 15% protein, 30% fat, fairly standard typical macronutrient profile for the general population.

And these were otherwise healthy participants. But what was interesting was they did both isocaloric and hypercaloric conditions with the same contribution of total sugar intake at around 25%. And they looked specifically at body weight, liver fat, and circulating triglycerides. And what we could see is that at isocaloric conditions, there was no effect of even fructose in isolation or glucose.

There was just no effect of either monosaccharide type at 25% at a quarter of total daily energy in the context of isocaloric. I e energy balance levels of dietary intake of overall energy intake. And that was for body weight, for liver fat or for circulating triglycerides. And then in the hypercaloric conditions, these all rather predictably increase; there was an increase in body weight, there was an increase in liver fat, there was an increase in circulating triglycerides. But there was no difference between either type of sugar. So again, in a wider conversation, which isn't necessarily for today, that what this was showing was that there was really an equivalence between fructose and glucose, right?

The effect of the sugar over feeding was not dependent on the monosaccharide type. It was simply the contribution of excess sugar to total daily energy intake. But those effects were not observed for any outcome when energy balance was maintained even at such a high added free isolated sugar intake.

Danny Lennon: And that seems to be pretty consistent across the whole literature base. If I'm correct that when we see any substitution analysis of fructose for any other sugar in these isocaloric conditions, you don't really see an effect. And there's been like multiple meta-analysis kinda looking at this substitution analysis where you pretty much see the same thing across the board.

Alan Flanagan: To be fair, although I think the "sugar is benign, hashtag calorie deficit" line is not necessarily entirely representative of the evidence overall because we can see differences as we discussed with the Melin and colleagues studies earlier related to carbohydrate quality per se. But the sacred cows of honing in on a on a really negative effect of sugar and trying to allege that sugar has unique properties that are dysfunctional for cardiometabolic health. Those sacred cows tend to be that it increases visceral fat, that there's this increase in triglycerides that increase in

triglycerides will increase fat in the liver, and that will promote insulin resistance both in the liver and peripherally.

And we will get all of these. And not only that, that, but that this is what is argued to suggest that it's the knock on effect of the impact of sugar on triglycerides that causes LDL to remodel into small, dense particles, and that it's those small, dense particles that are the result and more atherogenic profile for cardiovascular risk.

But this is where they'll try to tie it back to sugar rather than other components of diet. And really, when we take all of those sacred cows and we stratify these well-controlled interventions along the lines of whether they were energy surplus or energy balance, they literally all fall by the wayside for the most part.

So whatever additional nuance may be there related to whole grain versus refined grain on some postprandial metabolic markers, a uniquely deleterious effect to sugars, added sugars or free sugars in the absence of energy balance is really not evident for these important endpoints that people like to focus on when they're alleging that sugar has a particularly negative effect on cardio metabolic health.

Danny Lennon: Yes. So let's focus in on that. If we do turn our attention to cardiovascular outcomes. And I just want to expand on what you just said because this really is at the crux of many of the conversations in this area related to triglycerides or to this atrogenic lipoprotein phenotype. And you've already just touched that there, that we know in circumstances where, let's say we already are dealing with someone who has an elevated LDL cholesterol, and even if they're at a normal weight, we know that a high triglyceride level is probably not going to be a good thing. And so this is the context where you say people will turn to sugar as something that is going to elevate these triglycerides is going to lead to this atherogenic lipoprotein phenotype and therefore that's how it's having this impact. So just because it is important, first of all, can you just again, clarify for people specifically what the atherogenic lipoprotein phenotype is and then when it does come to sugar and these high intakes of sugar and people will say, look, they clearly are going to increase triglycerides and lead to this phenotype this has to increase cardiovascular risk some way, just to emphasize that point you made.

Alan Flanagan: This is a kind of an interaction. So typically the pathway is described, and again I'll simplify, but with added with sugar intake, added sugar intake, it is proposed that there is this increase in triglycerides. When that increase in triglycerides goes over a certain point around 1.5 to 1.8 milli per liter of triglycerides, particularly once it's getting over those higher levels. Basically what happens in terms of postprandial metabolism is lipoproteins that carry triglyceride, like VLDL end up offloading that triglyceride onto LDL and HDL.

They're basically dumping ship in the postprandial metabolism period. And what ends up happening is LDL ends up remodeling into smaller, denser particles under the burden of this excess level of triglycerides. So these small dense particles are typically more able to penetrate the artery.

And then HDL, which is reverse cholesterol transport, typically returns to the liver under the burden of these excess triglycerides, but is itself metabolized in the liver. It's broken down by the liver. So we end up with lower HDL, with higher LDL, but particularly this increase in the particles that are small and dense.

And we've got high triglycerides. And this trifecta is known as the atherogenic lipoprotein phenotype or atherogenic dyslipidemia. And so it is very much mediated by levels of certainly postprandial triglycerides. And there's implications for metabolic health because if we're having such enough regulation in triglycerides synthesis, we're typically seeing an increase in intra hepatic triglycerides in the, in the triglycerides that have to be stored in the liver.

And that in and of itself then leads to insulin resistance in the liver. There's then knock on effects for fat spillovers Roy Taylor's twin cycle hypothesis that fat starts to fill into the pancreas and other visceral depos. So this is this kind of what's known as this clustering of cardiometabolic, cardiovascular and metabolic risk factors.

And this, we have good mechanistic understanding that these processes do occur. However, much of the focus on the, as I guess on the idea that it's simply sugar driving triglycerides and everything else flows from there is not necessarily as clear cut because it doesn't really take into account dose thresholds at which we might see such an effective sugar.

And secondly, in terms of current understanding, that picture has discounted the effect of fat, particularly on, on the levels of fat in the liver. And we have really good research now and we've just discussed one in the Parry and colleagues study showing that any effect on this postprandial picture is not going to be independent of dietary fat, and it's not going to be solely a result of sugar.

But certainly we can discuss why it would be, or what the evidence would suggest ef sugar would have what effects sugar would have on kind of postprandial triglycerides and what dose thresholds might have been identified.

Danny Lennon: Yeah. So when we think of sugars and fructose in particular, because it does get a lot of attention and you've highlighted how this plays into this possible accumulation of visceral fat, and that's one of the mechanisms that's pointed to the big question then is around these dose thresholds that you've just brought up there.

And one of the meta-analysis that you've highlighted as being particularly instructive for people in this area might be the one from Livesey & Taylor, which was a meta-analysis of intervention studies. So in relation to this question of fructose, the type of intakes where we might see some of these potential problems and then placing that in the relative context for what we've been discussing today, what are the main things that you could, you can take from that analysis that you think are quite useful?

Alan Flanagan: Yeah. I think this is one of the best synthesis of evidence in this area; controlled human feeding studies. They looked at triglycerides, both fasted and in the postprandial period. And they also specifically then considered whether fructose was "free fructose"; the isolated monosaccharide or whether it was "bound fructose", which is typically what we have in the food supplies.

So most of our sugar, table sugar for example, is sucrose, which is a fructose bound to a glucose molecule. So that's bound fructose. And basically what they showed in this synthesis of controlled feeding studies, was that it would take doses of free fructose, not bound fructose of over a hundred grams a day to increase fasting triglycerides, but that actually doses of around 50 grams could increase postprandial triglycerides, and there was no effect on body

weight and there was no effect on triglycerides at doses that are more habitual to population intake.

And there was actually a beneficial effect on HbA1C which is one of these properties of fructose, is that it leads to, in a more immediate sense, less of a postprandial glucose glycemia response. But coming back to these doses of fructose, and we mentioned it was free fructose. So if we were to say that a dose of 50 grams of free fructose, increased postprandial triglycerides to really get to that dose by consuming the sugar we have in our food supply, would require a dose of a hundred grams of total sugars a day.

And there are certainly subsets of the population that are consuming these levels of added sugars of free sugars. But ultimately as well, like over the 50 gram threshold, there was a little bit of a dose dependency but it really wasn't anywhere near what observed in terms of postprandial triglycerides for fasting triglycerides.

I think there's some interesting stuff here that does suggest that we can certainly have this effect of fructose on postprandial triglycerides that's probably more relevant than the increase in fasting triglycerides, that dose that would increase postprandial triglycerides is lower than the kind of dose that at which there was effects shown for fasting triglycerides.

However, to contextualize it against the sugar habitual in our food supply, we need to factor in that, that would be bound fructose were consuming, and that those levels again are likely consumed in, in a subset of the population as opposed to habitual levels of intake.

Danny Lennon: One of the other meta-analysis that kind of sh looks at some of these outcomes was one from Evans and colleagues. Again, a similar picture here; 11 trials close to 300 patients, I think. And you see virtually for the outcomes they looked at least there, whilst there might be slightly statistically significant differences in some of them not in others, there was basically no real clinically meaningful differences in most of the markers they looked at.

When you have this substitution of fructose for others did that analysis or did any others that come to mind highlight anything different? Or do you think

there's a pretty consistent pattern from what you've just described with the Livesey and Taylor?

Alan Flanagan: Yeah, I think it's fairly consistent. Like they did a substitution analysis where they were looking at, say, the effects of free fructose at doses of less than a hundred grams. Whether fructose replaced starch or sucrose or glucose, pure glucose there was no increase in fasting. In fasting triglycerides at these doses of less than a hundred grams.

Now, if you were over 100 grams, they showed that you did get a greater effect on fasting, triglycerides if fructose replaced starch, but not sucrose. So ultimately, again, this kind of general principle is that this the sugar type, they seem to have equivalent effects, whether we're talking about sugar like sucrose or fructose or monosaccharide glucose.

And I think, the substitution of one sugar for the other is potentially less relevant than just the actual level of sugar as it relates to the level of energy in the diet.

Danny Lennon: Excellent. So I think that rounds out for that particular aspect related to cardiovascular disease, but we can focus in maybe specifically on blood pressure. And there's been a few different studies and a few different analyses that have attempted to hone in on blood sugar as well as some other aspects like blood lipids, which we'll maybe mention that might be instructive. One of those is a systematic review and meta-analysis from Fattore and colleagues looking at free sugars impact on blood pressure and lipids.

And again, they took a meta-analysis of intervention trials specifically, and they were looking at diets that had a given amount of energy from free sugars, compared with control diets of the same amount of energy, which is important here. So we have 28 studies in this overall, and by and large, the take home on the blood pressure front is really not much, that there's really no real difference in terms of their impact on systolic or diastolic blood pressure when you have this free sugar substitution for complex carbohydrates there.

And then there's a whole bunch of stuff on the lipids, which we can get into, but it's, some of them end up once you have some of the subgroup analysis

accounted for, some of those differences in lipids tend to fall away. And so in, in short, it seemed at least based on the Fattore study that, again, a similar picture as we've been outlining so far, that there's not really a major difference when you compare these higher or lower free sugar diets in the context of matched energy and without this overfeeding situation per se.

Alan Flanagan: Yeah, the blood pressure findings were basically null, but for LDL cholesterol replacing sugars for complex carbohydrates, i e removing complex carbohydrates, adding sugar was associated with an increase in LDL of about seven milligrams per deciliter.

But that seemed to be where the actual level of energy exchange was like around 25%. In order to tease that out was one of the subgroup analyses. Or when there was high total calorie intake. Overall, I just I don't think it was a particularly a resounding verdict against sugar. We do know that it can have deleterious parameters that we described earlier, but this is in the context of iso energetic diets now, and we're really not seeing much of an effect even when it's replacing complex carbohydrates.

Danny Lennon: So maybe to bring some of this full circle we said, Earlier on, we had these three studies from John Kirwan's lab, and of course we'll discuss a third of them now because this brings us back to the question of not sugar, but this comparison between whole grains and refined grains, which we've touched on a couple of times now.

And in one of their 2016 RCTs, they had a look at blood pressure specifically here. So as we've described already, we have this randomized crossover setup. These whole grain and refined grain diets, which by and large are the exact same in energy and macronutrients with the, on the exception being fiber, just due down to the different amounts of whole grains and refined grains here.

And the rest of the methodology, as you've said, is pretty much the same now here with relation to blood pressure as one of the outcome. We do see some differences that were detected with a decrease of 5.8 millimeters of mercury after the whole grain diet, whereas a decrease of 1.6 after the control diet.

Again, this is where, depending which way we want to interpret this, you could have two different findings. Right on, on one front you have this

threefold greater reduction from the whole grain diet. But we have now a situation where even despite this high refined grain intake, you're still seeing this very slight but albeit still a decrease in this refined or controlled diet.

So again, it really depends on what way someone is going to try and interpret this. But by and large, we see benefit for whole grain, but not necessarily a complet. Falling apart of health with the refined grain. So similar to some of the findings from earlier.

Alan Flanagan: Again I thought that the change in lipids was interesting. So for our total cholesterol on the whole grain and refined grain diet that decreased by 20 milligrams at 11 milligrams per deciliter respectively, of which LDL was 14 milligrams and seven milligrams lower on the whole grain and refined grain diets respectively. So again, yes, we could say, okay, there was an improvement on the refined grain diet that may relate to weight loss.

Nevertheless, there's clearly a greater magnitude, much greater magnitude in relation to whole grains. Triglycerides decreased by about 10 milligrams on both diets. There was no difference. Which, which again may speak to the fact that. In kind of people that aren't metabolically impaired unless there's a big contribution at of sugar and overfeeding like de novo lipogenesis may not necessarily be any sort of major contributor and certainly in this case not at all as far as an equivalent decrease. But yeah, it seems like if we're comparing refined grains to whole grains rather than just isolation sugar it. All of these studies from John Kirwan's group really do suggest advantage to whole grains.

But you're not going to die of metabolic or cardiovascular disease necessarily from consuming refined grains. It's just that the magnitude of improvement in the context of an energy deficit would not be as much and that probably is relevant then when we think about free living context and long-term.

Danny Lennon: Yeah. I think that is something we'll circle back to in the pragmatic conclusions, but is important to keep in mind that this is certainly not something to say, it doesn't matter that you don't need to care about any of this stuff, just match calories of macronutrients. In fact, it pushed back to that of indeed you could have situations where, yes in particular with this trial, there was actually weight loss in both groups.

So you can probably see that's why there's this decrease in blood pressure. And so someone could say, "look, my health isn't getting worse", but that is discounting that you are missing out on. Potential health promoting effects of diet that you're missing out on by avoiding whole grains, let's say.

So it's certainly not a recommendation to say it doesn't matter, which I think sometimes is the conclusion people can come to right, of as long as we're not in a calorie surplus, it doesn't matter about sugar, about whole grain, et cetera, which is certainly not the case. We'll get to back to that.

Very briefly, maybe we'll just tick this off because I think this is one of the buzzwords that comes up in terms of outcomes in relation to this, is around endothelial function. One of the studies that think came to, to highlight this was one on cocoa; Nijake and colleagues, I'm probably getting that name wrong, 2011. This is from the team at Yale; so Penny Kris-Etherington, David Katz and others were authors on this paper.

You have 44 adults. Again a BMI range of 25 to 35, so overweight and obesity class one. Randomized control trial. Again, crossover design, similar to many of what we've des described so far. Six week diet interventions, four week washout, followed by the other dietary intervention and now the this in particular, we had these three different treatments. There was a sugar free cocoa beverage. There was a sugar sweetened cocoa beverage, and then there was a sugar sweetened cocoa free placebo.

While they're obviously looking at the effects of cocoa, for our purposes here today, what we're really interested to see is well, if there's a difference here between adding the sugar sweetened beverage with cocoa or the sugar free. Now of course for their interests around cocoa, they find that the two cocoa drinks relative to the one without cocoa had an improvement in endothelial function as measured through flow mediated dilation.

But when we look at the difference between the sugar free and the sugar sweet and coa beverage, there was a maybe slight difference, or at least it was trending that way. I don't think it reached statistical significance in the end. In both cases, there was an improvement in this flow mediated dilation with those cocoa beverages, whether they had sugar or not.

Although maybe if we look at those slight changes, there was a trend for greater improvement with the sugar free cocoa beverage. But certainly the sugar didn't cancel out the hypothetical benefit you would get from that cocoa drink, at least in this specific outcome of flow media dilation. So that is, is one that came up in that area. don't know if you've any comments on that particular study or indeed any others with this general outcome of endothelial function?

Alan Flanagan: To contextualize what is this outcome and why is it relevant? This is a non-invasive way of testing like responsiveness by basically restricting blood flow blood pressure cuff and inflating it. Basically looking at the response of the artery in the arm and its ability to dilate. So it's expressed as a percentage. And what's interesting is that there do appear to be meaningful correlations with lower cardiovascular risk. So there's been a couple of meta-analysis that have shown that for each 1% increase in flow mediated dilation, the risk of cardiovascular disease events might be up to about 12% lower.

And so what we saw in this was that the sugar free cocoa had a change of about 2.4% from baseline, an increase of 2.4%, and the sugar sweetened cocoa had an increase of about 1.5%. So this is about a 0.9% difference between the two. And I wouldn't simply extrapolate that by saying if there was a 2% increase, that must be a 25% lower cardiovascular disease risk.

That's not necessarily how that would work. And also the use of the brachial artery. And the upper arm might overestimate the effects because it's a smaller artery. It might overestimate the the effects. But nevertheless, what I think was interesting is the magnitude of effect and increased flow mediated dilation was similar to what we see in other cocoa studies.

We know that cocoa flavanols have a particular effect on blood pressure through increased nitric oxide synthesis and vasodilation. But while there was probably just that effect in isolation of the sugar-free cocoa, yeah. Again, there was still a benefit on the sugar sweetened cocoa.

It's just the magnitude was slightly was slightly less. Yeah, again, it's not a, it's not a resounding verdict against the addition of sugar to cocoa. Whether someone wants that for a cold winter night.

Danny Lennon: So that brings us maybe to getting to some conclusions. And I think first it would be remiss that we don't mention that there's obviously typical recommendations given in different dietary guidelines for different countries or for different organizations, whether that's to do with diabetes or heart disease, et cetera.

And by and large we see many of those fall with a kind of general guideline. Sometimes, again, depending where we're looking of maybe 10% or less of calories. More places now pushed towards 5% for that maximal risk reduction. And these are type of limits that seem to be set again, depending on where we're looking.

Again, to clarify, we're talking here about free sugars within the diet, not sugar in fruit, for example. That needs to be limited below a certain amount. And with regard to this, it's probably worth thinking about what types of levels do we see in the population? And then beyond that, just thinking about what does it mean to have these limits?

It's certainly not that there, there's no difference at all in no matter how much sugar you have, as long as it's within a certain range. And foreseeably, we could see a difference between a diet that has 10% from added sugars, and in diet that is 1%, but by and large we're thinking at a population level we see these recommendations 5% for maximal risk reduction, typically some then 10% as a general guideline. So with that, how does that kind of typically compare to maybe what we might see in the population? And again, this is going to very much depend on the population looking at, but how far away are we generally from getting to these types of thresholds?

Alan Flanagan: A little bit so NDNS data, which is National Diet Nutrition survey data in the UK. And National Health and Nutrition examination survey, which is NHANES data in the US indicate that average added sugar, these non milk extrinsic sugars intakes in the population are anywhere between, say, 11 and 13%.

So relative to how one defines the ideal threshold to be reached, that's clearly not that far off, 10% or lower. But it's a little bit further off 5% if that's the target. That 5% threshold typically is set with dental caries in mind particularly in children. So it potentially might be more relevant in the context of childhood and adolescence to aim for that 5%.

But nevertheless there is some daylight between population averages and the 5% threshold, less daylight if we wanted to get people below 10%. And importantly, certainly from a cardiovascular disease mortality perspective really see the risk take off over about 20% of energy. And so that typically only represents about 5% of the general population.

So this is important ecological kind of relevance to consider when we certainly think about the sugar over feeding studies. But particularly when we consider the isocaloric studies. And I think we really say that when we look at population habitual intakes of foods the foods that contribute the most to daily energy we do typically see that these foods are not necessarily only high in isolated sugar.

The effects of sugar sweetened beverages on adverse health outcomes is now, I would say well established and accepted. But the other foods that would be to now that's an example of where we can isolate a specific component of the diet that is just added sugars. But the rest of the diet typically is comprised of foods that are a mix.

And so they're high in fat, they're concomitant high and refined starch and added sugars and or added sugars. So in terms of the levels of current population intake there's certainly not a cause for as much a cause for concern as if sugar intakes were up around, 18-20% perhaps or more.

There is potentially the relevance of if it does contribute a substantial proportion of daily intake that there could be an effect on metabolic health as far as postprandial triglycerides go. That could be relevant at levels of current population intake. But overall, I think these studies do indicate that the real effect of sugar in a free living context when we factor in the wider evidence and not just the isocaloric studies we've discussed today, that real effect of sugar is in its contribution to energy excess, it's in its contribution, therefore to increased adiposity, the knock on effects associated with increased adiposity and chronic energy surplus.

And I think that's really the role of sugar in the food supply is as a characteristic of diet that drives energy excess in the population. But at current thresholds of intake are we particularly worried about its cardiovascular and metabolic complications independent of that weight loss? I would say the data does not support that kind of conclusion.

Danny Lennon: Yeah, and I think that's really important to get to that pragmatic conclusion that you've outlined there of on one hand Yes. To speak to our initial question. In situations where we don't have this caloric excess, it seems that most of the detrimental health impacts that we see with high sugar intakes tend to fall away either completely or mitigated to a large degree or completely disappear. And so it seems to be in that context. But if we think about some of these conversations online and the potential for someone to go too far the other way or spread a message that is maybe even problematic is that someone could be of this opinion, oh look, don't worry about sugar.

That's only ever a problem in hypercaloric situations. Just it's not an issue. That could be taken up the wrong way because as you noted in the real world, high sugar intakes do lead to hypercaloric diets. They do lead to over consumption and they do lead to then all these this myriad of impacts that we see from that.

And so that is what's happening. And feasibly, when people try and limit the amount of added sugar within the diet, that leads to a whole host of probably positive changes. By and large doesn't mean they have to completely eliminate it, but some of those changes to get below those threshold, we mentioned probably not only reduce sugar, but as you outline, reduce probably a whole bunch of other things and that's probably likely beneficial.

And one of the other important considerations is that even if we say sugar isn't the devil, and even if we do take a situation where there is no hypercaloric diet, let's say someone stays within a certain range, they're not gaining weight, they're eating at a certain number of calories by default, the more and more they increase a portion of added sugars that are contributing those calories, the calories that have to be reduced from somewhere else.

So they have to buy and large eat less of other things, which contain a whole host of other beneficial nutrients and can have positive health outcomes. I think that might be the piece that gets missed sometimes.

Alan Flanagan: Yes. That really is it. Unfortunately the effect of adding sugars in the diet is that they're added without compensation adjustments in wider energy intake. And that's where the problem arises. And particularly where they do come in the form of like sugar sweetened beverages that is they

typically just added to the diet as an extra with no change. So, we could say that perhaps the role of sugar is indirect in many respects, in the context of overfeeding, but that it is easy to create conditions of overfeeding with a high intake of added sugar. And I think for most people in the population, that it can be easy to make some of these changes because they're simple food swaps. It's replacing a sugar sweetened beverage with an artificially or non-calorically sweetened beverage.

These are straight up food swaps that can be obtained. And as it relates to perhaps more nuanced conversation, like the role of refined versus whole grain, maybe not necessarily just sugars, there, there are likely to be benefits derived for a whole range of reasons with food substitutions along those lines as well. But I think that the real kind of adverse effect of sugar is in its role. Being added to the diet without any compensation alterations in energy intake.

Danny Lennon: I think often when we get to pragmatic conclusions, one thing we often end up emphasizing is the importance of considering the totality of diet and the overall average dietary pattern. Someones follows, and this is no different here, that if we were even to say we were to, for health reasons, keep within a certain limit of added sugars within the diet. Based on those recommendations we've just outlined, again, someone could reach that in two different ways, which would likely have a different impact.

We could have one of the maybe pitfall of the reductionist focus that we've mentioned before of they don't look at the overall diet. They instead focus in on just sugar and I'll get this as low as possible, and you can go out and find a whole host of low sugar or sugar free products that then that person consumes without any other focus and you could eat within those limits, doesn't really tell us about if the overall diet's healthy. On the other hand, someone could probably not really need to think about how many exact grams of sugar is my average diet. That's probably not a calculus most people need to do. Instead they need to think about the overall diet pattern. That we've often discussed before.

And by including more of the things that are health promoting, that just leaves less room for the types of high intakes of sugar that are likely going to come along. And so that's a way where you're feasibly meeting those

guideline recommendations for sugar intake, but working from a bottom up perspective, as opposed to just honing in on sugar itself.

So yeah, there's two different ways that someone could reach those limits, or those thresholds. The only other thing I think is worth mentioning is probably not relevant to general population, but is com comparing that to, let's say athletes or others, is just how huge of a modifier of risk exercises, particularly in the context of sugar intakes. And so this is one place where we see exercise interventions have huge differential impacts and how much that would modify the level of intake within someone's diet that could feasibly cause problems or not. And maybe that sometimes gets overlooked in diet only conversations.

Alan Flanagan: Yes, if you're going to eat sugar; Lift things!

Danny Lennon: And so maybe to finish that means that by and large we can say that in general, most of the deleterious health impacts of excess sugar intake in the dire are generally caused by the caloric excess and fat accumulation that comes along with that.

But that is not to say that the conclusion is therefore, that your goal should be to add as much added sugar to your diet whilst keeping within a certain number of calories. That's probably a very misguided way and is certainly not a health promoting dietary pattern that you end up with. So be weary of the two extremes at the end of this conversation.

Yes, that is it. Thank you to everyone for listening to this episode from both myself and from Alan. We hope you've enjoyed this and you can get, of course, any links. Papers that we've mentioned and any additional material in the links that are appearing in the description box where you're currently listening, and we hope you continue to listen to future episodes.

So that is it from us. Thanks for listening and we will talk to you again in the episode very soon.