Transcript

Danny Lennon: Welcome to Sigma Nutrition Radio. You are very welcome to the podcast. My name is Danny Lennon alongside me today is Alan Flanagan and Niamh Aspell. And today we're going to be talking all about artificial sweeteners and cancer risk specifically through the lens of a recently published study. And so this comes off the back of a question that was sent into us from one of our Sigma Nutrition Premium subscribers.

So if you are a Premium subscriber, you can leave a question in the AMA section of the members area, and that will either. It covered in one of our AMA episodes or it might serve as the basis for a full podcast episode as is the case today, because this particular question is a big enough one that would probably be worth covering in a full episode.

And so this question came in from Zachary and he asked: *"What are your thoughts on this recent publication? Adjustment model, follow up time, contrast and exposure, et cetera, all appeared sufficient."* And the study that Zachary links to is one that has actually caused quite a considerable stir online in various news outlets, on social media, et cetera.

And many people have pointed to this. Many of you listening may have came across it. And it's a study looking at artificial sweetener intake and cancer risk

off the basis of the NutriNet-Santè cohort study out of France. So this particular paper was published in PLOS Medicine in March of 2022. As I just mentioned, it got reported across the media all types of media sites that typically report on the findings of studies.

And as you may suspect, as is a common thing, unfortunately, that you will have came across. And that we've probably mentioned before is that unfortunately, when the media gets hold of certain studies, they can go jump to conclusions that are probably something that worries people more than the actual studies should.

So it's either a misinterpretation or it's a scary sounding headline, or even when they're just stating an association, it can sometimes to the reader seemed like it's something terrible without putting some further context to it. And so hopefully we're going to try and do some of that today. So you would see online in places them talking about artificial sweeteners are linked to cancer risk. Artificial sweeteners are going to increase your cancer risk by 13%, which was the particular finding of this study. And then you'll see in certain places; there's one site I came across, I believe it was studyfind .org And within their article the opening paragraph starts with *"if you think picking a packet of zero calorie Splenda is going to let you have your cake and eat it too, think again. New research from France reveals that consuming common artificial sweeteners can increase your risk for cancer"*.

And so of course, this has caused a considerable amount of interest online as this. Obviously a study in humans. This is one where people are saying *"Hey, I've heard all this stuff about sweeteners before. And yeah, I heard maybe the previous episode where we have this, a lot of this data is in mechanistic work or in animals. But what about this? Here's a human study. It seems to be done really well. And we're seeing this increased risk of cancer. What's the deal?"*

So that's what we're going to talk about today. And indeed it is come from a reputable group. Some of the authors on the list of author's names that you'll see are ones that have probably popped up on studies that you've read before we referenced here; Emmanuelle Kesse-Guyot for example or Mathilde Touvier have been authors on papers that we've discussed on previous episodes. And also for those of you who are regular listeners, you will know back at episode 431 of this podcast, we did an overview episode on artificial

sweeteners and human health. Once section of that was looking at cancer and we made the point that up to this point, there's been relatively little human evidence supporting the fact that there's any degree of causality with sweetener intake and cancer. Most of the cancer claims are based on rodent data that hasn't been able to be shown in humans.

And we also noted a bit of the nuances that the difficulty of extrapolating rodent data to humans on this specific particular outcome in terms of like metabolism and other aspects. So now that we do have this study, that is from a reputable group done in humans and is showing this increased risk, what is the deal?

So we're going to work our way through it. And like we said, that this is the NutriNet-Santè cohort that this particular study had over 100,000 people in it. And the kind of big headline is that on an overall basis, artificial sweetener intake compared to not consuming artificial sweeteners, leads to a 13% increase in cancer overall.

And then there's some other results related to specific types of cancers and then to different sweeteners, which we will discuss. So with all of that preamble, maybe let's get into this. And at this point, I'm going to hand it over to you Niamh to walk us through the study design and some aspects bew, be related to how the study was set up some of the methodology and the initial things that people should be aware of in relation to this particular study design.

Niamh Aspell: I think initially going off the back of the last podcast we did on this, I think this is one of the better designed studies. And a lot of the research in this area is animal models. So this does provide good new evidence in humans. So with this particular study, what they aimed to do or what their objective was to investigate the association between artificial sweetener intake.

What's different from this one in terms of what they mean by artificial sweetener intake is beyond what a lot of the other studies have done. So a lot of the other investigations into this have looked at consumption of artificial sweeteners, but just specifically, traditionally, specifically to non sugar sweetened beverages. So ones that were like your diet colas and stuff, they didn't consider most studies didn't consider total dietary intake. So we know

that artificial sweeteners are added to lots of things, particularly now as a lot of like off shelf products are being reformulated so that they have a lower sugar content.

So they're in a much wider source of food and drinks that we consumed day to day. So this study wanted to give a better overview of total consumption of artificial sweetener intake. So they went into quite a lot of effort to determine those other dietary sources. their objective essentially, was to look at that overall consumption and cancer risk.

They wanted to look at overall cancer risk. So any type of cancer that was identified in any of the participants over the longitudinal study, and then also site specific cancers and the analysis was all predetermined. So this this population study was first set up and I think in April, 2019, and they pre-specified all of the different parameters they were interested in and what different research questions that they were going to try and answer in the study.

So this is a part of that pre-specified protocol. They went into like much more detail in terms of determining the artificial sweetener content then than other studies did they collected dietary assessment? So 24 hour dietary recall, this is an entirely web based cohort. So they have these online modules, people can sign up, they advertise quite widely.

It's a study for older adults, but it's from the recruitment kind of age of 45 is the eligibility criteria for this study and had rolling recruitment since 2009. So they're actively still recruiting people. It's quite low in terms of the age profile for an older population type study, they usually go from 45. So it's still quite young group, but they collected their data every two years. But for the first initial study for the first initial like baseline visit, they did a 24 hour dietary recall they would do the 24 hour dietary recall. Picking two (non) consecutive days; one day at the weekend and two during two during the week, but they were at random. So the participants didn't know when they were going to have to do that. So non-consecutive days, sorry. And they were randomly assigned those over 15 day period. They, had photographs in terms of validating the portion sizes or whether they were standard serving sizes. And then they validated all of the dietary collection again, using interviews or trained dietitians.

I can maybe talk a bit more in while around the validation using blood and urinary biomarkers. And they took a baseline of participant intake essentially for the first two years. So all of the dietary records that they recorded or collected over the first two years, they took an average of those to determine their artificial sweetener intake.

They did a lot of indepth analysis and we might get into a little bit more around determining the content of artificial sweeteners in particular food groups. and then for determining cancer cases, so people were followed up, there was an annual health questionnaire and they collected medical information, different treatments that they had during that period, if they had any major health events.

And if they did report that they had a cancer, then that was further followed up by a physician. And if they needed to corroborate that again, they would get in contact with the participants physician as well. So they were they, the particular outcome of the study. And then they acquired an indepth statistical analysis.

They looked at lots of different features within the groups, but they did a cock proportional hazard model to determine any the associations between the intakes of artificial sweeteners and cancer risk over an eight year, period. I think that was one of the question. One, one of the points that in the question as well, was that it seemed like a sufficient period of time. It was a good period of time. I'm not sure if it was sufficient in terms of follow up for cancer risk in people who are reasonably healthy and quite young, but essentially their main was that there was an association between consumers of artificial sweeteners and cancer outcomes. They broke down the consumers slightly differently.

So they have people, a large proportion were non artificial sweetener consumers, and they broke it down to people who didn't consume artificial sweeteners to low consumers and high consumers. And then they did a cross analysis. That way they ended up looking at two different prostate and breast cancer because they were the most prevalent cancers that were reported during the study.

Danny Lennon: Certainly if we start with maybe the dietary assessment, because dietary assessment, as we've discussed in this podcast before is

something that often comes under a lot of scrutiny in many epidemiological studies of nutrition. So it's probably worth lingering on for a moment.

And so maybe I'll put this to you Alan, when you were looking at some of the aspects of the dietary assessment here, Quite interesting in this particular study, can you maybe just touch on not only some thoughts that you have about that for this study in particular, but maybe they didn't even link that back to a more general case of what characteristics around dietary assessment methods that are employed in an epidemiological trial can give us more or less faith when they're used and how you think this study stacks up. So are there any particular things that struck you about dietary assessment methods used?

Alan Flanagan: I think even for people that are interested in nutrition, research methodology and certainly epidemiology, I think a lot of people would probably reading this. See the fact that the dietary assessment method was based on 24 hour recalls and they might think, Ooh, this is a limitation.

And so it's important to distinguish between the general use of 24 hour recalls and what they're designed to capture versus the traditional use in well executed cohorts of food frequency questionnaires the main difference being that food frequency questionnaires, the conceptual exposure of interest that they're designed to capture is average intake over time.

And so they're not designed to capture your intake necessarily that day or your intake. Even the previous month, the whole concept is it's average intake over time. And that's distinct from 24 hour recalls, which are aimed to. Generally speaking, one of their positives is that they're, open-ended, they're quick to administer.

They're often suitable in low literacy contexts. They're easy to administer and they're not burdensome on participants, but they're yielding contextual information about that particular previous 24 hours. And so, as a result, they typically haven't been favored to use as the measurement instrument in cohort studies.

They have been used primarily as the validation or calibration instrument, but the NutriNet-Sante cohort is slightly different. And is not necessarily

using 24 hour recalls in the traditional context as just that isolation capturing the previous days. Intake, for example, typically interviewer led by a trained dietitian and there's methods techniques that are used perhaps the most famous is called the multiple pass methods.

And so that's where someone's going through a 24 hour recall with someone saying, what did you have for breakfast? And they might say cereals, and then you keep you do multiple passes that, oh what did you have with those cereals? Milk? What type of milk? Low fat, high fat? And so on and so forth to try and put together a level of granularity that actually makes for a more meaningful analysis.

So this particular cohort has not used 24 hour recalls as a calibration or validation instrument, it's used them specifically as the measurement instrument. But the approach that they have taken like Niamh outlined is they take three non-consecutive days. So they're taking 3x 24 hour recalls over generally a two week period that captures two week days, and one weekend for day to day variability.

But then they're also administering this every six months. And so what they're essentially doing as a way to think about this rather than necessarily capturing average intake over time is they're capturing an average snapshot across a particular timeframe. So a snapshot into January a snapshot in June, and then they're averaging that snapshot out over the timeframe of the particular study or the number of 24 hour recalls that a participant has completed now, while this is a more sophisticated approach to the use of 24 hour recalls, specifically as a measurement instrument and not as a reference instrument, it still introduces the potential for high levels of random error.

So difficulties in the actual measurement assessment itself, and also the systematic error in nutrition, epidemiology that we tend to know of is to underestimate intakes, which has an influence then on the ultimate outcomes. So there's essentially, there's more of the two main types of error that you would be trying to minimize random and systematic. And there's more scope for those errors with the use of 24 hour recalls, even where they're using two weekends and one weekday. The aim of doing say a weekend versus a weekday is to, based on the assumption that people would have slightly different dietary intake, maybe during the week on the weekend, but you're still introducing a lot of within person variability and

where you have high within person variability in a large cohort, there's a lot of variability then from person to person. So as Niamh said, they've obviously conscious and of the fact that they're utilizing a method, an entirely web-based cohort that isn't necessarily The more traditional approach of using FFQs they've undertaken quite extensive validation, both against a questionnaire administered by a dietician, a 24 hour recall administered by a dietician.

So that's using that kind of method we were describing where you actually sit down and you really tease out someone's intake. And they've also validated against biomarkers, and they've also undertaken additional lab analysis to actually quantify the levels of the artificial sweeteners and other food additives that are exposures of interest that they've looked at in this study.

I think the main thing that I would, and we don't have this data, as far as I can see for the artificial sweeteners is questioning what the correlation between the. Measurement in this case, artificial sweeteners and the actual assessment of intake is, and they don't report that in the paper. There is another paper from this cohort, which looked at the correlations between the intakes of commonly consumed foods as assessed through their 24 hour recalls and blood biomarkers.

And they were okay. But they weren't necessarily at the maybe higher end of where you might want to see a correlation coefficient for a nutrient exposure. So. I think this is a really well executed cohort study that just in general, NutriNet-Sante have really well designed and executed cohort studies. And the publications that come out of it are very well executed and thought through in terms of their quantification of the exposure, the statistical analysis and otherwise. But I still would have some degree of trepidation over the potential scope for error, potentially with the 24 error recall approach as the measurement instrument, particularly where the correlations between other more habitually consumed fruit, like foods like fruit or fish and the biomarkers were not as strong as you might otherwise want assessed. So I think there's a lot of positives to this cohort, but I still think there's potentially a few limitations to the dietary assessment method that particularly when they're really breaking novel ground with this assessment of artificial sweeteners just we need to hold those two things in tension I think.

Danny Lennon: Let me ask you just to maybe expand on one thing that you raised there just preemptively as I think it might be interesting for people to consider of you noted that the 24 hour recalls can be attempted to be validated against biomarkers. Can you maybe just explain, maybe given an example of what does that actually look like? What are we discussing there, when we talk about validation against biomarkers?

Alan Flanagan: As we discussed with Dr. Austin Baraki, biomarkers are markers that we would measure in the body, and for example, the blood or adipose tissue that are correlated to dietary intake, and there are a number of things that make for a good nutritional biomarker, particularly for nutrients, that for example, would not be endogenously synthesized in the body and that we would require an external source for.

So as an example of what I mean, when they're correlating say foods to a biomarker, you would look at the assessment of fish in the 24 hour recalls. And then you would look at measured levels of EPA and DHA, potentially, for example, in plasma. And you would look at how strong your assessment of fish intake in the 24 hour recall correlated with what is supposed to be the more objective biomarker assessment of EPA and DHA in plasma.

And you would look at how strongly those are related. And you could do the same for say vegetables and vitamin C in the plasma as well. And again, this opens up potentially extra layers that I don't think we need to get into because for example, DHA might be a better biomarker than EPA because EPA can be converted from ALA. So there's all these extra layers to what makes a really robust biomarker. But yeah, so, so that's essentially what we mean by validating something against a biomarker. And usually cohort studies will take a food frequency questionnaire and validate that against either a number of repeated 24 hour recalls or potentially a seven day weighted measured food diary.

And they would look at how well the measured diet from the FFQ correlates with these more, these reference methods. But like I said, the nutrient sane cohort has used 24 hour recalls repeated every six months as the measurement instrument. But. It potentially still introduces some issues in relation to within person error and some other errors of dietary assessment that might be more magnified with the use of FFQ with 24 hour recalls, even though they're still repeating them.

Danny Lennon: One of the other things that I think is worth drilling down into Niamh, that you had already raised, is the assessment of artificial sweetener intake specifically, because there's a few bits of nuance to this. Can you maybe get into some of those details about how exactly they attempted to go about quantifying some of this and then some of the interesting elements of that assessment?

Niamh Aspell: I think just one other point on the dietary assessment ... they established their baseline by looking at those first two years of dietary records, which would equate to a total of 12 records for participant. But the average was actually quite low. They only had five on average for the participants.

And I think another thing that probably doesn't hold strong in it is almost 20,000, so I'm not sure if we've mentioned, I think there's initially 128,000 available for this study. It ended up being around 100,000 included, but 20,000 of those were over under reporters on their dietary intake. So a really large proportion of them were removed from the study sample at the end because they were under reporting. So it of just highlights another kind of massive limitation in terms of employing a 24 hour recall is there's typically a number of flaws in it, in that regard. But in terms of quantifying. There's just one other thing as well than the dietary assessment. So they're looking at the first two years, but if you compare that with some of the other data that they collected in within the start of the study, like the baseline profile of their participants, a much larger number, I think it's almost double the number of participants who reported being on a diet in the last two years were also the higher consumers of artificial sweeteners as well.

So I think there's, that needs to be considered in this too, that potentially this population, they decided at that particular point, for some reason, whatever, it's not reported in this, what their motivation was maybe to go on that diet and whether their artificial sweetener intake began at that point as well.

Was it because there was a particular health reason or a pre-health condition that they felt like I need to lose weight or I need to change my lifestyle a little bit? So that's not reported in it. And I don't think there's any assessment of change over time in their dietary recall. So we don't know if their artificial sweetener intake changed dramatically between those first two years.

It's just the average values, but we don't know how it changed over the course of the study as well. They didn't report that anyway, in the particular in this particular paper. But I think another point you've touched on it as well. Alan is these are single time points. So if you're going to collect a dietary recall for somebody out like particular like holiday periods, like during the Christmas period, when people are on holidays and they've changed their normal pattern, I don't know it hasn't said it in any other protocol, whether there was a, Predetermined question before you complete your recall saying, are you currently, following your life as normal, are you still, going to work this week or, are you still following a normal kind of routine?

I'm not sure if they've, tried to understand that more and if they haven't eliminated anyone if they have. So I think there's lots of important things like that also need to be considered. And when it comes to the biomarkers, the actual correlations were quite weak that they found when they were conducting some of that analysis.

It's presented in the paper like they did validate that with everybody, but that was actually a previous study within this cohort group back in 2015, where they took less than 200 people and they validated their dietary records against urinary and blood biomarkers. So things looking they're written veg intake and does it, so they kind of correlate with the level of vitamin.

So I think there's a lot of strength in what they're reporting, but there's also some kind of weaknesses in how it's been applied slightly, but back to the quantifying, the artificial sweetener intake. So they were really rigorous in this particular, in their approach to this. So obviously there's very commonly known artificial sweeteners and then there's other products, lots of products now have added artificial sweeteners. They had reported that aspartame is found in nearly 1400 food products on the French market, and there's more than 6,000 worldwide. So it's in quite a lot of foods. So they wanted to understand based on the consumption patterns.

These particular participants going by the brands that they had reported that they were consuming, they would then use food composition tables based in those two from the population in France. And then there's one global data set that they use. So they cross reference all of the food products that the participants had consumed.

And they also did that. They went one step further and they cross referenced them. They called it, I think, dynamic referencing. So there's change over time in terms of. Composition of the product. So they factored in, if there had been any reformulations of particular products over that two year period and how that differed in terms of the level of artificial sweeteners that were included in that product at different time points.

So they were really particularly rigorous in that regard. And then they did a separate lab study. So they had developed a large number of lab assays, where they were able to then test and measure directly measure the dose of additives contained within a large number of primary food sources as well.

They evidenced a list of different artificial sweeteners that were currently. Available within these particular foods. I won't go through the list. I think there's maybe seven or eight of them, but most of them more than half of them were quite negligible in terms of their contribution to their intakes. And they ended up then specifically just looking at three. So they looked at aspartame, at AceK, and as sucralose. So they focus and they're the most commonly consumed artificial sweeteners, but they grouped in terms of total artificial sweeteners. They grouped any amount into that one category for total consumers.

But when it came to the analysis, they looked at those who consumed lower levels. And then those who consumed higher levels of artificial sweeteners, they still They still had a large proportion of people. It was over 50% of the contribution of artificial sweeteners in the diet was from soft drinks.

But it does highlight that all of the previous studies were only potentially factoring in for people who do consume that they're only looking at 50% of their potential exposure to artificial sweeteners as well. So in terms of a dose response in that regard, I think this definitely really adds to the data.

I think their motivation for this piece of work is that EFSA are reevaluating the safety of artificial sweeteners at the moment. I think this adds quite a lot to it because you can, to a certain degree extrapolate those findings against the other studies that have currently been conducted as well.

So I think all of the participants in this study were consuming the aspartame and the three that I'd mentioned below the daily intakes of, I think it's 40

milligrams per kilogram of body weight for aspartame, then they were all consuming below that. So it wasn't that they were extreme consumers, but they did have a proportion of people that fell within that high group of consumers.

And they did quite a lot of in depth analysis, looking at, if you're a high consumer of artificial sweeteners, but you don't consume high levels of sugar or below the recommended intakes, which I think, or they cut upper limits of a hundred grams per day compared to then people who eat sugar, but then have no intake of artificial sweeteners as well.

So they did try and decipher a small bit there, I suppose they put artificial sweeteners and sugar on the bench together in that sense to see if one was worse than the other, in terms of concert outcomes.

Alan Flanagan: Yeah and I think, it'll become more relevant as we start to work our way through the results. But I think one of the most crucial things to point out about this study is that 65% or nearly 64% of participants did not actually consume or were not recorded to consume artificial sweeteners at all. So the vast majority of this cohort in this analysis were not, were in the category of non-consumers and that included aspartame, ACE, K, and sucralose.

So it's just something to note as we start to move forward and discuss the results because the reference category for this cohort is the vast majority of the overall cohort who were. Assessed as being, as Niamh said, they categorized people into non-consumption low consumption or high consumption.

They also did a separate analysis in the, which is in the supplementary material where they just had non-consumers versus consumers with distinction between high versus low consumers. But it's really crucial to recall that in, in this analysis, it's not like the majority of the cohort were all stratified, according to some level of consumption, the, flat, nearly three quarters of the cohort were down as non-consumers which may be odd or seem to be odd. But and certainly doesn't seem to reflect health because when we look at the Cova, its associated with high levels of artificial sweetener consumption, they tended to be people who were healthier, younger on a diet and these kind of things.

But I think it's really important to note that actually the vast majority of this cohort are essentially in the analysis as the reference category of not consuming any of these main three artificial sweeteners that were of interest. And then of the specific sub sweeteners. The majority the highest percentage of participants consuming were both aspartame and AceK.

So about 20% consumed both of these sweeteners, but for sucralose, for example, only about 0.4, 5% of those who were consuming artificial sweeteners consumed only sucralose. and, 6% consumed aspartame or sorry, no participants consumed aspartame and sucralose. So I think that's just really important is the vast majority of this cohort.

We're not even consuming artificial sweeteners. And that will be important when we start to discuss the kind of reference category and the comparisons made.

Danny Lennon: Yeah. So, so there's actually a couple of things that I wanna reemphasize based on what you just said and what you, you said Niamh as well, that will re here later when we discuss some results and also implications one is just to reiterate what you've outlined there, Alan, that within these three categories that we can break down people into of non-consumers low consumers and high consumers.

We have a majority of two thirds or more than being non-consumers, which Quite surprising, right? Like the whole thing about looking at the safety of artificial sweeteners is because it is such a how ubiquitous it is within our food supply of oh, we really need to make sure that this is safe, but here we're seeing a group where the majority of people don't seem to consume any of these, which is quite strange, but I think might speak to the actual demographics and characteristics of this population as we'll probably discuss later on the second thing that was really worthwhile to note that I'm sure we'll come back to in the conclusions is something you mentioned Niamh is around.

If we see where the artificial sweeteners were coming from in people's diets, unsurprisingly, most of it was from soft drinks, but still it was only 53% of their total intake was coming from these artificially sweetened soft drinks. And given that typically. Most other studies nearly always use something like

artificially sweet and soft drinks as a proxy for total artificial sweetener intake.

That kind of sheds an interesting point on how we should maybe look at data backwards as well as data that will come in the future. And then one of the final things that you also noted was that we had this 20,000 people excluded on the basis of under reporting. And so maybe just to finally cross that off before we get into the results just to clarify exactly what's gone on here for people, you said there was 120,000 people.

Originally we have a roughly around 20,000 get excluded for under reporting in terms of energy intake. And there's some ways that we can a arrive at working that out. Can you maybe just clarify that point for people of what we're really saying, but under reporting here and why that's excluded on what basis and why that is essentially done.

I just wanted another

Niamh Aspell: point on the artificial sweetener, the. General prevalence of it within this group, they do also report in the paper that it's a, it's pretty much like 50% less than the prevalence rate of the national estimates of consumption. So there is, it does really flag that this particular group aren't representative of the gen the general population would in France.

But I think they did. So this very kind of typical procedure that's done in these types of studies or any kind of study where they use a 24 hour recall, ultimately from the 20 hour, 24 hour recall, you can establish somebody's daily energy intake with this study. They also calculated or got people's assessments.

So they were able to establish their BMI. So they were able to work out what their basal metabolic rate is. So based on their kind of, their agent and their current weight. And if that didn't corroborate. With the dietary intake, there is particular methods it's called a Goldberg cutoff method, which is based on mean pop mean population biases reported in energy intake.

So they can establish that quite easily, looking at, essentially what your energy is and what your energy requirements are. They cross reference that

as well with what your activity levels are. So they conducted an IPAC assessment or see how much physical activity you're doing in a day.

And if that didn't corroborate with the number of calories that you're reported to eat on a daily basis, they would establish a cutoff point and exclude those participants from the overall analysis. Maybe

Danny Lennon: it's time to start digging into some of the results here. And with that, it might include talking about some of the methodology around cancer case diagnosis.

So in this study, we. A bit over 3000 cancer cases being diagnosed. And then I suppose the, those headlines that we've already mentioned talking about this 30% increase in risk is talking specifically about the positive association between artificial sweetener intake for those high consumers versus non-consumers and the risk for overall cancer.

Now, then there's bunch of other results we can maybe get into some of where we're looking at specific sites of cancer. We can look at different types of artificial sweeteners, but from an overview level that those headlines are coming from this 13%. Increase in risk or this hazard ratio of 1.13, between artificial sweetener intake in total and the risk of overall cancer.

So maybe we can start working through these, maybe I'll turn to you first, Alan, from the results beyond that kind of headline figure. Is there anything interesting or of note or what are the main things that jump out that we should maybe flag for people in the

Alan Flanagan: results? Yeah, so I think there's potentially a couple of ways we can think through it one and again, this is a strength of the study is like Niamh said that their assessment of artificial sweeteners is hands down the most robust to date in any certainly observational nutritional epidemiology research.

So there are hazard ratios for the low consumers and high consumers compared to the non-consumers and they're calculated both for total artificial sweeteners. And then for aspartame, ACE, K and sucralose specifically each of those individually, because they're the most three commonly consumed in the population. And then each of those four

quantifications of the exposure of artificial sweeteners are then compared for all cancers. So as cancer overall and then breast and prostate specifically. And then there's also then obesity related cancers. And again, that they're, I think it's important to highlight that they're fully adjusted model accounted for a really comprehensive range of potential factors that could be associated with the outcomes specifically as we're talking about cancer here.

So they had weight gain during follow up, for example, had physical activity levels. They'd smoking status number of cigarettes in pack years. And then from a nutrition perspective, there were. Lifestyle related or anthropometric covariate as well. I just named them as an examples.

And then for diet, they had, alcohol sodium, saturated, fat, total energy intake, which is really important when we're factoring in potential. Other associations that might explain some of the outcomes and then, for specific cancer outcomes breast cancer menopausal status and factors like this added in.

So, so there, there are adjustment models and their statistical analysis is really robust. And there's a fairly dizzying array of that. We, are presented with I, I think that if we start to. Look at them in both these four outcomes of overall breast, prostate and obesity related cancers to, to try and maybe synthesize this.

What we tend to see is the statistically significant associations are for either total artificial sweeteners, aspartame and ACE K for overall cancer, but no associations for sucralose. And then for obesity related cancers, we see the exact same thing where there are Significant associations for total aspartame and ACE K, but only for ACE K for example, in their unadjusted model, when they added all the adjustments in that was no longer statistically significant.

Although the direction of effect was still evident, but again, not for sucralose. And then if we look at breast and prostate as. The specific outcomes, the results are more inconsistent for prostate cancer. The direction of effect appears to be similar to what we've seen with the others. But they're not statistically significant associations at all for any, for either total artificial sweeteners, aspartame, AceK or sucralose, and for breast cancer, again, similar direction of effect.

But once adjustment is factored in with these other variables, then only aspartame in the fully adjusted model retains its significant association. And so this is ultimately. The kind of top line of the findings. But this in and of itself raises some important questions that we need to start to think about exposure, outcome relationships.

One of which, for example, is, and I've had a conversation with a, a couple of people that are more in the cancer research side of things about this. And I think the overall cancer end point is a little problematic for multiple reasons. We're assuming that there's just the same, kind of pathogenesis of all of them, even though they have unifying characteristics, which is why they're called cancers.

But I, I think the composite overall cancer's endpoint is potentially something that can get diluted by. By a range of factors that are cancer, specific factors, one of which need mentioned earlier is even duration of follow up in, in a relatively young cohort. And then the obesity related cancers is interesting in so far as again, the prostate and breast specific associations are relatively underwhelming in the case of prostate cancer none of them are statistically significant in the case of breast cancer. Very little of them survive adjustment except for aspartame. But for obesity related cancers, many of them remain significant after adjustment for those factors we talked about, particularly aspartame and this leads us to consider one of the most well established critiques of the artificial sweetener epidemiology, which is the potential for reverse causality.

Now their model has adjusted for BMI and weight gain over time. But we also know that there's a relationship between artificial sweetener consumption, high levels of intake and adiposity and higher levels of adiposity, which does bring this into play. And we know as Niamh mentioned that there's this kind of prevalence with dieting, but we don't know whether weight loss was intentional or not intentional.

And that's a really important factor when we're thinking about epidemiology of weight loss. So yeah, when we look at these kind of four outcomes, we've got overall cancer, which I think, a lot of people probably more in the cancer research side might. Have a few reservations about the use of overall cancer as an endpoint in any study, like in, in independent of nutritional

epidemiology for various reasons, because of the multifactorial nature of each specific site and condition.

And then for breast and prostate, largely. Findings that are not statistically significant or certainly don't survive adjustment with the exception of aspartame for breast cancer. And then most of the other significant findings other than overall cancer are for obesity related cancers. And this brings in a big issue of the potential for reverse causality.

That has been a major issue in the artificial sweetener epidemiology, generally speaking, although their models did adjust for BMI and weight gain over time in the study. I still think there's some interesting, further things that we can pick at here but I think one major potential limitation for the most part that we need to consider is what's been highlighted already, is that a strength of this study is identifying food sources of artificial sweeteners, 50 odd, 3%, maybe half of artificial sweetener intake coming from. Artificially sweetened beverages. But what would've been interesting to see is, and I, again, correct me if I'm missing. This is if they had actually separately quantified rather than just the artificial sweeteners, the risk associated with the food sources of those artificial sweeteners, because yogurt, for example, is not just aspartame, it's the sum of the food matrix. And I think that when we look at that contributions to the total artificial sweetener intake, it might have been interesting to see some sort of, subgroup analysis. Relative to the food sources. But yeah, that's the kind of the overall summary, most of the thrust of the significances in relation to overall cancers and for obesity cancers, although sucralose showed no significant associations across any of the outcomes.

Niamh Aspell: A really important thing to highlight is that there's a very low rate of cancer incidents in the cohort as well. So only three, just like less than three and a half thousand incidents of cancer cases were diagnosed over that period. I think the average age of the population, I think contributes to the low incidents there as well.

But in those who were diagnosed over the eight year period, they're more they're around on average, 10 years older than the average age of the cohort. So they were a small bit older. I think looking at the results, looking at those tables of the differences between the low consumers and the high consumers. And they were then, compared to the non-consumer group, it's

quite obvious. If you look, you can see quite a trend that people there's a higher risk of cancer in the low consumer group compared to the high consumer group. So it maybe reflects that there's something else potentially going on.

It's not just the artificial sweeteners or if there is some form of dose response there. But I like, I'm not entirely sure that they can justify or say that, but I think with the level or the number of people that are reported to, to have cancer in this study it's quite low. And if you actually look at the numbers in a lot of detail, not in a lot of detail, but if you just, if you calculate the rate of cancer within those on average, it's around 31 and every thousand of the participants who consume no sweeteners were likely to have a diagnosis after eight years. And then if you look at the numbers, I think there was like 65,000 odd in the non-consumer group. And 2000 of those still went on to develop a cancer. And then with the others, if you look at those figures, those who consume the higher amounts on average, it would equate to around 32-33. So there's very small difference in terms of numbers. So it's obviously it's still, one or two extra, people's still, it's not negligible, but it's still, not a large difference in terms of instant cancer rate.

And then if you think about, so there's quite a few, I know Alan's described all of the different adjustments that they made when they were doing this analysis. There is like a level of margin of error there, but it means that, there could be, between one and one and 10 say cases, additional cases on those who consume the higher amounts if you consider the error, that could be the difference between the actual and projected results that you're usually found in these survey type data. So there is unpredictability in this data as well, but we don't have much margin for unpredictability. Given the case rates didn't vary like a massive amount.

So I think that's important. I think we need, they need to, maybe they didn't so much touch on the point that it was low consumers who actually were reporting the kind of higher risks of the cancers rates as well within that group. So I think that's. Something that was maybe slightly overlooked.

And then with the adjustments, they did make good adjustments. I think it would've been interesting as well. If they considered medication use at the start of the study, they did do medical history, but they kept that to certain

particular medical outcomes. They didn't necessarily go in and look at the medication use of this group.

So if we're talking about this age this cohort age of, midlife, you're looking at, determinants of pre diseases, who's more likely to become sicker. And I think having an idea of the medications that they were taking at that time, would've been interesting. When it comes to, I think the, one of the points of the question that was raised by the listener as well is around the adjustments.

And I think there needs to be maybe more description in this when reviewing these types of studies about what the residual confounding. is and how it is, and isn't addressed. So there's lots of other, confounding factors that were, potentially not considered in this particular study. And if you attempt to adjust for those, it can make it a massive difference in the outcome, because there's small. So such small number of differences in the cases between those as well. Obviously it's a very large sample size, but the incidence rate within that sample size is quite low. It might have been more interesting if it was a high risk profile group, as opposed to the profile that we have in this cohort, which is typical of these kind of cohort studies, just, it's not a flaw of the study, it's just the nature of people who typically come forward to take part they're usually a bit more proactive, in their health and have a better health status. Very large proportion of this study. I think three quarters are female as well, highly educated. The list of the normal kind of. Upper end of this sociodemographic profile.

So I think that's my main kind of standout from looking at this was the, it's not a clear trend, the more that you're consuming sweeteners, that you're more likely to develop any of the cancers that are listed here. And I do think they'd quite a rigorous way of reporting the instant cancer rates as well. They had physicians look, look over that and double check and then go back and talk to the GP or the doctor of the actual patient as well. So they were, they, the researchers worked hard to collect the data and to validate as best they can given the sample size.

Alan Flanagan: I think that comes back to, we mentioned it's really rare in any cohort study to have such an odd stratification of your exposure in terms of intake let's say, for example, we're looking at a study, that's looking at red meat consumption, whether it's divided into kind of tert lesi or quintiles of

intake, which the latter of which would be the norm for a lot of nutritional epidemiology, you're typically going to have a kind of broader distribution of that red meat intake across those quantiles of the exposure, whereas here, we've got against the vast majority 64,000 or 65,000 of the 102,000 in the analysis are reported as non-consumers.

And as, as Niamh said, and it's such an important point to talk about, what's the actual case rate in this group. So we've got a really low number of cases, which is going to just weaken your overall statistical power to detect effects. But if we look at the actual difference, so, and Niamh just mentioned that low consumers often had an actual higher hazard ratio than the high consumers. They also just then categorize participants dichotomously as non-consumers or consumers. And again, you look at that for total cancers. You've 213 reported cases of cancer in the non-consumers amongst 64,901 participants. And in the consumers, you've got 1,345 reported incident cases of cancer.

In a group, a total group of 37,976. So as a percentage event rate in each of those groups, that's 3.5% in the consumer group. And 3.1% in the non-consumer group, these aren't enormous differences. And I think, yeah, that's a really, just a hammer home, the point Niamh just made for listeners that really factors into this analysis, even though they're getting a hazard ratio that appears to be, a 14% increase in cancer risk, a lot of the time these aren't particularly precise effect estimates. If we look at the confidence intervals and that's going to reflect a very low number of cases and quite a distorted number of participants in the kind of in the reference group. And overall there, there's not huge differences between the incidence rates in consumers.

And non-consumers, if we think about the number of cases relative to the number of participants, so that if we start to think about the base rate incidence of these outcomes in the population, then those factors like Niamh mentioned the actual age of people who did get cancer being on average 10 years older.

So like all of these factors come into tempering I think the enthusiasm with which some of the findings have been reported certainly in the popular or the lay media

Danny Lennon: And a number of those points fit together and are worth reinforcing of whilst this difference that we've just noted is we could say is actually quite relatively small, whether as Niamh outlined, if we look at 31 out of every thousand for non-consumers versus say 32 or 33 per every thousand or as the percentages that, that you gave Alan of 3.1 versus 3.4%, we could say, look, these are very small differences. Of course we could make the point of this still has the potential to be meaningful once you scale it up to a population level.

But the point I think that we're making is that when you have something that is. Small difference and then layering on top of it that these are not exact figures, right? We're taking a small incident cancer rate, which we say can be problematic or leaf leaves the door open for there to be a bit more measurement error.

And then even though the adjustment model overall we said was like, pretty good. It wasn't so comprehensive that everything was a adjusted for. We could certainly point to some things and ne view gave some examples. So when you factor those in together, given the potential for some degree of measurement error, now these.

When there's only a small difference between the groups, then that can be more than the explained potentially by a measurement error. Right. So it's all these things come together when we're trying to interpret. What does it actually mean?

Alan Flanagan: I think what, just one more point that we were talking about the difference potentially between some of the outcomes are overall in obesity related cancers. One thing they make the point, the authors that obviously previous research has, there is this reverse causality issue with artificial sweeteners and adiposity in epidemiology as it relates to outcomes. But we've. We analyzed the interaction with BMI, which they did to be fair.

The issue is that in, in each category of artificial sweetener intake and the overall cohort itself, the average BMI was 23.6. Now that's not represented of necessarily of the general population. And there was no difference in BMI really across the categories. So, they had BMI then just classified dichotomously over or under 25.

And that was what they looked at for their interaction effect with total artificial sweeteners, as aspartame, AceK, and sucralose, and those four related cancer kind of outcomes. So none of them were statistically significant, but again, I don't know that's necessarily a true test of the potential interaction at, to completely wipe out the.

Reverse causality associations that we tend to have. If we have in a relationship between obesity and cancer, we know that there's a relationship between high levels of artificial sweetener consumption and higher adiposity, because people are conscious of, either minimizing calories or whatever.

We've seen that with previous epidemiology on this question not the cancer as an outcome. So I don't think we could necessarily entirely say that the reverse causality potential has been completely accounted for by this interaction analysis that they did with BMI defined dichotomously as either over or under 25.

Danny Lennon: So with those questions that we've raised, maybe now we can get to a point where we can start. Formulating some conclusion to answer Zachary's initial question, which was what are your thoughts on this particular study? And I think that encompasses two aspects, which I'm going to ask you both on first, when we're thinking about your thoughts on this study.

One aspect is your evaluation of the overall quality of this study itself. And then the second aspect would be what probably most people generally want as a interpretation from that of what are your thoughts on potential conclusions from this study and what that means pragmatically for our decisions about artificial sweetener use either at a public health level or as an individual consumer, trying to make decisions of whether to include these or not.

So, let me start with uni for your kind of concluding thoughts about this study, both on one as a study itself, it's overall quality and then two pragmatically, what you think is possible to take from this in relation to artificial sweeteners and

Niamh Aspell: cancer. I think overall the, this it's one of the better epi studies. I think it definitely adds to the data for ESFA for their reevaluation to a certain degree. I think. For EFSA they'll want to know how much artificial sweetener is, potentially detrimental to health. I don't think the study can tell us that because there's not a clear kind of dose response relationship and the findings that they've reported on.

I think they have adjusted quite well in models that they've used. They do have, obviously it's a nutrition based study. Overall this is just one outcome of the NutriNet-Sante study. so I think it's designed quite well in that respect. What we can take from it is that we now know that non sugar sweetened beverage is only account for about 50% of the artificial sweetener intake of the population and that going by just that alone, it's probably not adequate to look only at beverages in future studies. I think that's one good example. That's probably come out of the study is that it needs to be a little bit more robust in that sense. The baseline cohort. I just think when we stick with these kind of rules on open recruitment and we don't have more balance in terms of the demographic profile and socio profile of the groups, I think they're always going to be limited to certain cohorts of the population, which isn't beneficial to EFSA needs to be more more of a general understanding of how it affects all people.

And then again, just, there's so many kind of minor questions over the characteristics of the participant in this, in these groups, like the consumers were much more likely to be smokers diabetic, obviously, because it's an artificial sweetener, they were eating more ultra processed foods. There's obviously lots of other ingredients within ultra processed foods that can have a negative impact on our health.

So I think that's a small limitation on that. And the cohort was maybe potentially just a small bit too young. I think the follow up period was long enough if they had an older group within the population. So in terms of how to apply a study dietary assessment, we, it would be good if they reported the change in dietary habits over time.

And as a mentioned previously, if they had valid use this as a validation and had a little bit more of a robust measure in terms of dietary patterns, I think would've been quite good overall. I think it adds more understanding for the development of better design studies, slightly more robust studies in this

area. But it does follow the findings that we're finding on other outcomes. So when we looked at obesity related outcomes in previous studies, it still leaves a lot of questions.

Danny Lennon: A an, for your concluding remarks. If someone asked you for your thoughts in this particular study, what would you tend to leave people with?

Alan Flanagan: I'm going to echo what Niamh said in terms of, I've looked at the NutriNet-Sante cohort before in relation to some of the other outcomes that they've investigated. I think it's a really designed overall and their execution. It's a well executed work of nutritional epidemiology over with this study.

I think as Niamh said, they have really added a lot of methodological advancements for people to think about if they're looking specifically at artificial sweeteners I think for this particular outcome, I think it's really important to then always come back to the wider literature that we have.

Ultimately, these are compounds that are in the food supply based on extensive toxicology and safety data. All of the stuff we talked about in the previous episode If these findings are true, let's say they are an accurate reflection of this relationship between this exposure and outcome.

Then it would represent a catastrophic really failure of our toxicology safety and regulatory and monitoring assessments. So on that level, I think that these are findings that should absolutely be taken seriously. I think that there are still a number of potential issues.

Everything that we've discussed with the the numbers, the issues need talked about in terms of the age of the cohort, that for cancer specifically, potentially the duration of follow up not being sufficient. And these other factors all go into tempering. How. We would think of the findings from a perspective.

I don't think that we can obviously make any sort of claim in relation to cause effect. Of course not. I don't think we can even make a claim that this single study now represents the default assumption that we need to make about this exposure outcome relationship because of the wider research overall,

still supporting that these compounds are safe for consumption at habitual levels of population consumption.

But to me, what this study challenges is that latter statement. It challenges, the assumption that at habitual levels of consumption in the population, there is no risk whatsoever. And I think on that basis all of the limitations that we have discussed acknowledged it's still an overall a well executed study.

And as a result, those findings caveats and all do warrant, I think real consideration. And as Niamh said for and the reevaluation and the ongoing safety and toxicology monitoring programs, I think what this study does challenge is the assumption that there's no risk at current habitual population levels of consumption.

And I think that should be taken seriously. So for me, the implication really goes into back to the regulatory systems that we have in place to assess these products and one particular factor that. I think I'd highlight with that is, and we just discussed this during the artificial sweeteners podcast.

There were a group of in Italy who conducted three studies that purported to suggest that there was a carcinogenic effect of aspartame and evaluated those studies specifically. And this came out that well, they had used, they had misdiagnosed cancers. They had administered aspartame during fetal development, which I think, I don't think they had ethical approval for, there was all these kind of red flags over the conducts of the studies, but it seems that group actually had their data like reevaluated and the authors of the present study reference that.

In their discussion and so there's, even those studies have come back around a little bit to, to maybe suggest that there's a lot here that needs potentially further consideration.

Danny Lennon: So there, there's certainly a very welcome addition to the literature base and will certainly hopefully inform future research in this area, as well as future regulatory and policy making decisions. And certainly can be used in that vein, but for individuals or even practitioners right now what it's not to say is that this now is a paper that you can use as a way to say, or as an evidence based recommendation, I'm going to warn people off using any

artificial sweeteners. That is certainly not the case, but all the other open questions that Alan just outlined certainly remain.

So I think that will do us, I think hopefully that answers as Zachary's question and for everyone else, hopefully gives some context into some of the headlines you've undoubtedly seen since the release of this paper and hopefully gives you a look at how some of that can be evaluated. And that is us it for us this week.

Thank you for listening in. We will be back within our episode very soon. If you didn't enjoy this episode, please let us know. And if you'd like further episodes like this, where we're looking at a particular study that would be quite useful to hear and from myself from Niamh and from Alan, thank you for listening in, and we will talk to you another episode very soon and until then stay safe and take care.