DANNY LENNON: Mario, welcome to the podcast. Thank you so much for taking the time to join me.

MARIO KRATZ: Yeah, thanks so much, Danny, for having me. Really exciting to be on your 400 plus episode, I guess. Right? Congratulations for that.

DANNY LENNON: Yeah, I think we're at 408 in this particular episode, and there's a lot I actually want to ask you about. You've published some really interesting work in recent times in particular that we're going to focus on today. But I suppose before that, just to give some listeners some context about you, can you maybe give an introduction to your work over the years, your focus of that, and where that's kind of brought you to this kind of current point?

MARIO KRATZ: Yeah, so I'm German, as probably everyone has heard after your first sentence. I grew up near Bonn Cologne area in Germany, went to the University of Bonn, got a Master's in Nutrition and then moved to Munster where I got a PhD in Nutrition, doing basically a clinical study on the impact of different fatty acids on, broadly speaking, cardiovascular disease risk factor, but more specifically speaking, about concentrations of critical lipoproteins in the plasma, and also functional issues related to these lipoproteins and how they're affected by

diet, and specifically, the dietary fatty acid composition. Then I got interested in broadening that from cardiovascular disease to more obesity type 2 diabetes, because that was really, you know, so this is 18 years ago, maybe 20 years ago, it was really becoming clear that we're going to have major problems with obesity and type 2 diabetes all around the world.

And so, I moved to the US to Seattle to do a fellowship at the University of Washington with Dr. Scott Weigel, who at the time that just published some really interesting work on protein, high protein diets and the effects on satiety. And so, I was interested in expanding on that, came here, we did some clinical trials, really focused on the impact of diet composition basically, on all aspects related to energy homeostasis. So really focusing on why is it that we eat the amount of calories we eat every day. Obviously, that is affected to some degree by endogenous factors, I mean, who we are, how old we are, how much lean mass we have, these types of things. But I figured it's also almost certainly affected by the types of food we eat. So if we eat highly palatable food that are energy dense, we tend to overeat; and vice versa, if we eat food that's mostly leafs and greens, it's hard to overeat, right? So basically, asking questions around that was really something I was getting interested in. As I was wrapping that up, like, I started to do some work around glucose homeostasis as well, got myself a second mentor in Stephen Kahn, who is a well-known diabetes researcher here in Seattle. And that was really good to broaden into that area, simply because obesity and type 2 diabetes and also cardiovascular disease are so tightly linked, in many ways.

And so then, basically, after my fellowship was applied all around the world for a faculty position, and happened to get one here in Seattle at the Fred Hutchinson Cancer Research Center, not because obviously, I'd ever done any work on cancer – really, to this

day, I'm not particularly knowledgeable about cancer; but I found a faculty position in the cancer prevention program, and there was an emerging interest in trying to understand better the relationship between obesity and metabolic disease and many types of cancer, and they wanted someone who could look into those mechanisms, like, what are the mechanistic links really, and how does diet, you know, how does what we eat play into that. And so I've been at Fred Hutch – I always have to think about this – for 14 years, until just last June, when I decided to quit academia. And so, I'm just now establishing a new business that's going to be all around consulting, science communication, similar to what you're doing, really trying to up the standards in terms of what we know about nutrition as it relates to health and disease, in terms of actual evidence, as opposed to what we're seeing so much, particularly online and in book form about people just making up stories or building on their own anecdotes, and selling some product or some book around that. And obviously, happy to talk more about that, but that's going to be a side story today.

Leaving academia was a difficult step, because I always thought I'd be a professor and research all my life, but as you probably have heard from others, it's just really been frustrating to try to get funding for the types of nutrition studies, you know, well controlled feeding studies, where we're ideally providing all of the food for weeks and weeks or months and months at a time, and then do sophisticated phenotypic characterizations of participants, where we really not just drawing blood or getting their body weight, but where we're really measuring maybe their liver fat content, where we're measuring whether they have inflammation in the adipose tissue, where we're doing glucose tolerance tests, or DEXA scans. But these are all very expensive. And what I found is that, personally, I feel in nutrition we have a lot of fairly weak evidence from observational studies, we have some evidence from relatively

short-term feeding studies or dietary intervention studies in which we're mostly having fairly poor phenotypic characterization of people, often just based on fasting blood, for example, or body weight.

And I felt what we really need is a combination of longer term, good control of the diet, and the phenotypic characterization. And what I found in repeated attempts with trying to get grant funding with NIH here in the US, is that these types of studies are just very, very expensive, we're talking $4-5 million. And the pay line for those is like eight percentile maybe. So we're really basically spending, if you're devoted to this, you're spending most of your life working for the garbage bin, because you're writing grant after grant, and you do pilot study after pilot study, and then you never get the chance to actually fully do them. And through some of our clinical work, I've seen the impact that dietary change and helping actually people to change their lifestyle and their diet, what kind of impact that can have. I've had people starting to cry in these types of sessions saying this really changed my life for the better. And I just got fed up writing these theoretical grants where I felt like we already know so much, we got to help people discern the bullshit and the marketing from what really is out there that we know can help them improve the health. So that's really, in a three-minute summary, probably where I've been so far and where I'm hoping to go.

DANNY LENNON: Fantastic. And we'll probably definitely circle back to some of that throughout this conversation, I think, and it lays some very good foundation for what we're going to get into. As we mentioned at the outset of this discussion, the focus today is going to be on some of your work that you've published in the area of looking at low fat dairy versus high fat dairy, and impacts on cardiometabolic health in particular. Now, of course, we're going to maybe look in a bit more detail at two specific papers that were published about a trial this

year, however, your interest in this particular question far precedes that. And I think it is one of those questions that is very interesting when we start getting into the details because of, I suppose, people's presumptions about some of these food groups. So can you maybe just explain what it was about specifically, looking at these comparisons, and trying to answer these types of questions that first drew you to this topic in the first place?

MARIO KRATZ: Reflecting on this, I think it started about 10 or 11 years ago, maybe I had lunch with a friend of mine, who you actually know who's been on your call Stephen Guinea, who also lives in Seattle. And we were talking about what are really some of the gaps in nutrition, because I think, at least among scientists, there's already a lot of things that we agree on. But there are certain areas, I'd say, you know, meat is certainly one area, eggs and dairy are certainly, like, these are the big areas where there's disagreement, where some scientists are strongly of the opinion, the best human diet is probably dairy free or low in dairy. Others are of the opinion, well, yes-no, we can have some dairy, but it has to be low fat. And again, others are saying no, this is all wrong, we should really be kind of keeping foods as whole and unprocessed as we can, and we should have the full fat and fermented kind of foods. And I think that's really an interesting area to look into.

So what struck us was that the dietary guidelines in most countries on the world do recommend that people consume dairy, usually around three servings a day or so. And they very explicitly say consume non-fat or low fat dairy foods like non-fat milk, non-fat yogurt, low fat cheese, and stay away from the full fat things that are very rich in fat like cream, ice cream, butter and so forth. Stephen And I kind of both agreed that our casual reading of the literature didn't seem to agree with that, right, we both had followed the literature loosely in this field, and none of us could really come up

with strong papers that actually supported this. And when you read the guidelines at the time, it's said, the main reasons for really preferring low fat dairy were kind of threefold. One is, if you consume low fat dairy, then you remove basically the fat that doesn't have any nutrients. And the product will be more nutrient dense – nutrient density being defined as micronutrients per calorie, right? That makes sense.

Similarly, low fat dairy or non-fat dairy is less energy dense, right? So less kilocalories per gram. So if you drink a glass of non-fat milk as compared to, say, a glass of whole milk, you're going to get way less calories, and the logic here is, well, then overall, that will help reduce your calorie intake. And third, the thinking is, dairy fat, like much of animal fat is very rich in saturated fat, and cutting that out can only be good, because saturated fat increases total LDL cholesterol concentrations, as had been shown in trials with feeding people pure butter, and that would be expected to increase the risk of cardiovascular diseases. So I think this all sounded plausible, but we're very much aware of some studies that had actually looked at this, is full fat dairy consumption actually associated with heart disease, for example, is it associated with greater weight gain? And we actually knew that many studies did not show that.

So we decided to write a systematic review that was published in the European Journal of Nutrition in 2013, I think. And in it, we described basically the entire observational evidence, looking at specifically comparing full fat and low fat dairy foods with regards to weight gain and obesity, incident type 2 diabetes and incidence of different cardiovascular diseases. And in a nutshell, what was interesting about this is that what we found was really, if anything, the opposite of what would have been expected based on the very plausibly seeming assumptions that were underlying the dietary guidelines. And specifically, we found that most observational

studies actually find that the consumption of full fat dairy foods is associated with less weight gain over time, and a lower risk of obesity – something that's often not seen to the same degree for people who consume the most low fat dairy foods in these studies. And that an important thing actually I'd like to get to a little bit because that's often, even when I give talks about this topic, people misunderstand.

So in these observational studies, we're not really comparing directly full fat and low fat dairy foods, right? So it's not really possible in an observational study like this. What usually investigators do is they report associations for all dairy, they may just quantify basically total dairy consumption in, say, servings per day or grams per day, and then form quintiles and look, is there an association between total dairy consumption and say, obesity or weight gain over time. And then they may do this, again, just for low fat and non-fat dairy foods, and then again, for full fat dairy foods. Now, it's not directly comparable, simply because oftentimes, the people who eat say the most full fat dairy may also be the people who eat the most non-fat dairy. It's not mutually exclusive, like, I eat some full fat cheese, but I also eat some lower fat milk. Right? So it's a little bit difficult.

But from the studies, I'd say, very consistently, what we found is that the more favorable associations with regards to weight gain was seen for full fat dairy foods. And that's what we took from this, if you read the paper, nowhere in the paper – I think, I hope, at least – we don't say that eat full fat dairy and you're going to lose weight, we basically just conclude cautiously that the evidence currently from observational studies does not support the notion that consuming full fat dairy foods leads to consumption of excess calories and weight gain. I think that already was kind of unexpected, considering the considerations that have gone into the guidelines.

Then we did the same thing for type 2 diabetes, and again, we find that dairy products in general – actually, there's an inverse association with incident type 2 diabetes, so people who consume the most dairy foods, in general, tend to have slightly reduced risks of type 2 diabetes. And that's particularly the case for fermented dairy foods such as yogurt – a lot of interest in yogurt actually, and why that's so consistently inversely associated with incident type 2 diabetes, but also for full fat dairy products, at least, when we measure that consumption using a biomarker in the plasma phospholipids. Right? So when we look at an exposure, like, say, full fat dairy consumption, we can't simply quantify from a food frequency questionnaire how much whole milk and how much full fat yogurt someone eats. But there's also a biomarker or a few biomarkers that you can measure in the plasma phospholipids, and these are unique fatty acids that we find mostly in dairy fat, and it's been found in other studies that the people who have the most of these fatty acids in their blood had recently eaten the most full fat dairy foods. So they're thought to be by some a better biomarker, maybe a less biased biomarker of full fat dairy consumption.

And now in I'd say, six-seven different cohort studies, we've seen extremely consistent and extremely compelling inverse associations between some of these biomarkers, and incident type 2 diabetes, some studies suggesting in multivariate analysis, that the risk in people eating the most full fat dairy foods by this measure, have about 50% reduced risk of developing type 2 diabetes.

And lastly, in our study, we looked at cardiovascular disease. And again we didn't find what we should have been seeing if it was true that eating full fat dairy foods triggers cardiovascular disease. Because at the time, I think only one study had actually ever shown the positive association between full fat dairy consumption and heart disease. Several had found inverse associations. Most were not.

That paper actually got a lot of attention, and that's been interesting to me. I will be honest, it's not a great paper. I think it's nice, it's an okay paper, but it's not that amazing. But there's been so much interest in this in terms of the public and people tweeting about it, and that just really showed us there seems to be a lot of need for better information about this topic, simply because we seem to still be operating on the dietary guidelines level, and what people know, mostly based on assumptions. And that struck me is interesting, we do have some evidence, but we seem to just have disregarded the evidence and basically had our assumptions that these things should be true, you know, rule what we actually wrote into the dietary guidelines. So I was struck by that, and that really motivated me to do a randomized controlled trial in this field to get better information about these relationships.

DANNY LENNON: Yeah, there's so many interesting points throughout what you've just said, and I think maybe as a brief recap for people, one of the main points you've tried to get across here is that when we look at dietary guidelines, virtually across various different countries, it's common to see dairy produce not only as one of the core elements of that, but almost being viewed as essential, which is something that some people, as you note, will debate others, will be happy enough with that. But at the core of that is the recommendation typically for those to be low fat dairy products on a few different assumptions that theoretically, again, should play out, one, the energy density, because the fat component's taken out; two because there's a reduction, therefore, in saturated fat. We could think that that's going to have an impact there on LDL cholesterol levels, and therefore cardiovascular disease risk. And within those, it's notable then that you say, well, when we actually look at even some of the epidemiology or observational data, actually, with dairy in particular, we actually don't see that as strong as particularly other types of high saturated fat containing

foods, there seems to be something going on, at least, to put dairy on our radar of, well, why is this the case. You alluded to a few elements, I'm sure, we'll talk about later on, for the fact that some of them are fermented, we have different types of dairy that aren't equal and so on, that will definitely get to the course of this discussion.

But I think that perfectly sets the stage for the two papers that we're going to discuss today about the randomized controlled trial that he did. What I think was really cool to know about this was given that you said that you were first talking about that back in that 2013 paper, even now, when we fast forward to 2021, and this randomized control trial, from what I can tell, it's still quite unique in the sense that it's doing a really well controlled feeding study, looking at, in the first context, we're going to look at glucose tolerance, and trying to answer some of this question that is still up in the air that no other trial seems to have attempted to answer before, so that in itself is really cool.

So let's dig in here. There's two papers I'm going to link to in the show notes for people listening. The first appeared in March, that paper is titled the impact of diets rich in low fat or full fat dairy on glucose tolerance and its determinants, a randomized control trial. And that was published in the American Journal of Clinical Nutrition. Then in September, a second paper titled impact of low fat and full fat dairy foods on a fasting lipid profile and blood pressure was published, and this is also in the AJCN. So if we start with the first paper, looking at these diets rich in low fat and high fat dairy, and the impact on glucose tolerance, I'll let you introduce kind of some of the methodology here, but I found it interesting because we're attempting to look at really kind of two questions almost. There's the comparison of the low and the high dairy consumption or the low fat dairy and high fat dairy. But then there's also the comparison to will want in cases where we're limiting dairy.

And this, again, is really good to keep in perspective of when we're thinking about dietary guidelines. So maybe just in your own words, you'll do a far better job than I, can you maybe introduce this paper and how you would tend to set up and what was the question you're trying to answer?

MARIO KRATZ: I would like to actually, before I do that, I have one sentence about what you just said, because I think that's a really interesting one. And that is, there have been randomized controlled trials on this topic, and it's with regard to other endpoints like bodyweight. But interestingly, even though the observational evidence mostly points towards more favorable associations for full fat dairy, almost all the studies use non-fat milk. And I also said fermented foods like yogurt are very often seen very favorably in observational studies, but there's almost not been any trial with fermented foods. So what's curious to me about this is we always argue, we do these observational studies to form new hypotheses that we can then test in rigorous trials, yet we seem to be ignoring the observational evidence when we design these trials. So that was largely our motivation to do a trial in which we would compare not just a diet rich in dairy versus low in dairy, but also, as you said, for fat versus low fat.

So what we did is we decided to do this trial in men and women with the metabolic syndrome, because we wanted people to already have some disturbance in their glucose metabolism, they were maybe a little bit overweight which is the case usually there. And so, we recruited 72 men and women with the metabolic syndrome, and we first had them go through four weeks of a run-in period that was limited in dairy. So they were basically given just the dairy foods, and in that run-in period, that was limited in dairy, we gave them three servings of non-fat or skimmed milk per week, so about half a serving per day; and we asked them to consume only that in terms of dairy, not to consume any other dairy, but otherwise to eat

the normal habitual diet, just live their normal life. And then after four weeks, we brought them into clinic, and we randomized them to either stay on this limited dairy diet or to switch to a diet that contained 3.3 servings per day of either low fat or full fat, milk, yogurt and cheese, roughly one to one to one. So we ask basically people to eat one serving of milk, one serving of yogurt, and one serving of cheese per day as either non-fat or low fat version or as full fat version.

And then we asked them to do this for 12 weeks, and then basically assessed the changes in number of parameters, the primary being glucose tolerance as measured by a three-hour glucose tolerance test, right after the run-in period, right before the 12-week intervention phase and at the end of the 12-week intervention phase. And our rationale for picking glucose tolerance as the primary endpoint was that the most compelling evidence had been seen in observational studies, linking higher yogurt and higher full fat dairy consumption to a lower risk of type 2 diabetes. And with type 2 diabetes we're in the fortunate position that we don't have to do to wait for years and years, until someone develops the disease, like, say, in cancer, in a dietary study, to see whether the diet actually has an effect. Because in type 2 diabetes, we can directly measure the one clinically relevant outcome in laboratory tests, clinical tests. So we basically do a three-hour oral glucose tolerance test where we give people 75 grams of glucose. And then we can directly measure what their body's ability is to keep blood sugar levels in the homeostatic range in response to that standardized bolus of glucose.

DANNY LENNON: There's a couple of things that I want to get to because, like you said, there's some really cool elements to this, I really enjoyed reading it. One, just for people listening, something that you just brought up there just to make an extra clarification, you mentioned around this primary endpoint being glucose tolerance, and

you did that using a three-hour oral glucose tolerance test. Can you maybe explain to people who maybe have heard that but are not exactly familiar again, what this oral glucose tolerance test looks like, how that's administered, and then how that is transferred that into the results of calculating a glucose area under the curve?

MARIO KRATZ: So for readers who don't know-understand glucose metabolism and all the detail, one thing you need to be aware of is that in our blood, we usually have only about 100 or so milligrams per deciliter – deciliter being a 100 milliliters of glucose. And the body keeps it fairly stable for good reasons that's probably not going to get into today. So in all of your blood, in other words, that is only about a teaspoon or so of sugar. If you drink a beverage that has 75 grams of sugar, that's 15 teaspoons. So I asked my daughter just once, and I said, what happens if you drink this, and she said, well, obviously, the amount of sugar in your blood goes up to 16 teaspoons. But the reality is it barely goes up, in healthy people, it goes up from maybe 80 milligrams, 90 milligrams per deciliter to 120, 130, 140 maybe, and then it comes back down under the influence of specifically insulin. And so, the body really tries hard to keep the blood sugar level, the blood glucose level in that homeostatic range, I argue, from about 80 to about 140 milligrams per deciliter at all times in healthy, non-diabetic people.

So in type 2 diabetes, this gets out of whack through a number of factors, such that usually a fasting glucose is already elevated, often quite a lot, maybe to about 130-150 milligrams per deciliter. And then, as you consume a meal that contains carbohydrates, it may go to 300. It's still fairly low relative to the huge amount of carbohydrates many people eat, but it’s basically no longer as tightly regulated within the homeostatic range.

And so, in clinic when we do a three-hour oral glucose tolerance test, what we do is we put an intravenous catheter into people's arms, and they just lie still in the bed, and then we give them a beverage that has 75 grams of glucose. And they drink this in a very standardized fashion, like, we really, you know, the moment they put it on their lips, we put the stop clock on, and then they have to finish it within a certain amount of time. And then, after exactly 10 minutes, 20 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 180 minutes, a nurse stands ready and exactly at that second, when the minute is over, basically they draw a little vial of blood. And then we measure the change in the concentration of glucose and other related substances like insulin. As their body deals with this huge challenge of 15 teaspoons of sugar coming to their body and how then, what we basically are after is how well is the body able to deal with this challenge and how well is the body able to keep glucose within the homeostatic range; and we can quantify that by basically plotting the glucose concentration. Imagine a graph, where the x axis is time and the y axis is glucose, and you basically plot the change in glucose on this graph; and then what you can do is over the three-hour time period, you basically calculate the entire area under the glucose curve, and that gives you a sense of basically how glucose tolerant someone is – glucose tolerance basically being defined as the body's ability to keep glucose within the homeostatic range that is desired. So you can imagine that someone who's diabetic, the area under the curve of glucose, maybe two or three or four times as high as in someone who's totally healthy and non-diabetic.

DANNY LENNON: Fantastic. Before we get to the results, there was one other element that I really enjoyed that I would like to get to. So maybe just to recap, again, for people listening, as Mario has already outlined, we have this four-week wash-in diet period where their dairy consumption was limited to less than three servings of non-

fat milk per week. Then after that, we have a randomization to one of three diets for a 12-week period. We have one where people continue the limited dairy; one where they go on a diet of around three servings per day of full fat dairy in the form of milk, yogurt, and cheese; and then one that's three servings per day of low fat dairy. And so, the only difference between those dietary setups is just whether it's a low or a high fat version of those foods.

Now one really interesting thing that you included was a controlled feeding period, where the participants completed these five-day controlled feeding periods during which they were given all our food, and that happened once during the wash-in period; and then also, again within the intervention period towards the start of that. Can you maybe just explain the rationale for this, and how that was actually done practically?

MARIO KRATZ: So at the beginning of the podcast, I talked about how the dietary guidelines partly recommend low fat dairy, because the assumption is that with the lower energy density, you're going to eat less calories if someone eats low fat or non-fat dairy foods as compared to whole fat dairy foods, and we wanted to put that to the test. And to actually really know how many calories someone eats, you can't just ask them. We know from many examples that, particularly with regard to energy intake, questionnaires do a very poor job of telling us how many calories someone eats. So we figured we need to come up with another metric, and we have developed this basically protocol, where for some period of time we think, ideally, eight days would have been best, but five days is probably already fairly good. We give people all of their food, and we give them basically all of their food in excess of what we know they're going to eat, and then we give them the specific dairy foods, but they were randomized too for that particular period, and we ask them under all circumstances everyday eat your foods and eat

the other foods ad libitum. And so, when you now look at someone who would be randomized to the full fat dairy arm, they would first do this five-day period during the wash-in period, where we could measure, okay, if they barely eat any dairy, if their dairy intake is limited, how many calories do they eat, right? Okay, so let's say that number is 2000 calories, and now in the full fat area, we're giving them almost 500 kilocalories per day in the form of full fat dairy products – are they actually going to compensate for those calories? Are they going to eat less calories from other foods to make up for those calories? Or is their overall calorie consumption going to go up? Then we can put that in relation to the long term effect of the diets on body weight and fat mass, which we'd also measure to see, okay, if the actual calorie intake goes up during the five-day feeding period, then we would expect them to also gain weight during the 12-week intervention diet. Right?

DANNY LENNON: Very cool. So let's, with that, maybe move into some of the results, and there's a few different elements to this that are very interesting. Let's start with that primary endpoint of glucose tolerance. What were the findings after you've been able to collect the data here?

MARIO KRATZ: Yeah, so our hypothesis was based on the observational evidence, right? Strong inverse – very consistent and strong inverse association between biomarkers of full fat dairy intake and incident type 2 diabetes. We thought that we would see improvements in glucose tolerance, in both dairy arms, and particularly in the full fat dairy arm. What really happened is total null result, and what that means for those of you who don't usually speak this weird, clinical trial lingo, it just basically means you found no differential change in these groups. So actually, we never look at the change within a group because it's kind of meaningless, even though that's often done in trials, but there was absolutely no change. When we plotted the graphs, they basically look very, very similar,

before and after people consume the limited low fat and full fat dairy diet. So in other words, people's glucose tolerance was not in the least affected in these 12 weeks by whether or not they eat theory, and whether or not that dairy was full fat or low fat.

DANNY LENNON: With some of the secondary outcomes, and there's a number of these, are there any, in particular, that you found interesting or that are worth mentioning here at this point?

MARIO KRATZ: So I mentioned earlier, in a glucose tolerance test, we also measure insulin. And the reason for that is that insulin is the key hormone that, after a meal, that helps the body deal with the incoming glucose. The way this works is that as soon as you start consuming something that is sweet or has carbohydrates in it, the body senses that and the pancreas starts producing this hormone insulin. And you can think about the insulin basically as a key that opens kind of a door in the cells of the body, and then the glucose can go through that door into the cell. So in other words, with insulin around, the cells of the body can take up sugar from the bloodstream. And what we found with regard to insulin is that even though the glucose curves had not changed, the insulin curves did change, and they changed in a way that they were higher at the end of both of the dairy phases. Right? So basically, after consuming either low fat or full fat dairy for 12 weeks, people's insulin levels were higher, even though their glucose levels hadn't changed; and that can be interpreted as meaning that their body had become a little bit more insulin resistant, or, basically, the other way around, would be say is the insulin sensitivity had declined, not hugely, was fairly modest as an effect, but it was statistically significant and very consistent among different measures of insulin sensitivity. And that's an interesting finding in that, that wasn't really consistently described before in similar studies, and probably because most studies that were previously done, did not use this type of three-hour oral glucose tolerance

test, but instead just looked at fasting measures of insulin, so called HOMA insulin resistance index, which isn't particularly strong to actually detect these types of subtle changes in insulin sensitivity.

DANNY LENNON: So we're seeing insulin sensitivity being reduced in the groups that were consuming more of the dairy than the dairy restriction, which, as you point out, if we look at kind of maybe some of the epidemiology or observations beforehand, is kind of contrary to a lot of that. On reflection afterwards, what your particular thoughts as to why this may have been the case, are there any best hypotheses as to why you had this finding?

MARIO KRATZ: Yeah, so maybe we can do it in a chronological order in which we discussed it within our group, because when we first saw this, our first thinking was, well, there must be an explanation for this. Right? So maybe it's because people gain weight in these dairy arms, or maybe it's because dairy, as some people think, dairy maybe pro-inflammatory, maybe measures of inflammation increase, and inflammation is known to trigger insulin resistance, or maybe something about consuming dairy increased the amount of fat in the liver. And so, we looked at these endpoints, all of which were actually secondary endpoints in the trial, because they're major determinants of glucose tolerance, and we wanted to understand the effect of dairy on the entire pathway, basically, that is known to affect glucose homeostasis.

So with regard to weight we already discussed earlier, these controlled feeding periods. And so, we looked at that, and found that people did actually consume more calories, a lot more calories, when they were switching from the limited dairy to the low fat, and particularly the full fat dairy group. So when we looked at these five-day feeding periods, calorie consumption was – I have to look at the paper to actually know the exact number, but we gave them 500

calories or so in the form of full fat dairy, and almost by that much the total calorie intake increased. So there was a huge increase actually in calorie intake in the full fat dairy arm, a smaller one in the low fat dairy arm, and that was associated with weight gain, statistically significant weight gain in the full fat dairy arm of the study.

So that already, again, by itself, is an interesting finding, because to my knowledge, it's the first clinical trial that really showed weight gain on full fat dairy, as had been hypothesized in the dietary guidelines, but had never really been shown like that. And so, obviously, because weight is a major determinant of insulin sensitivity, we hypothesized, well, maybe it's the weight gain that actually triggered the insulin resistance. But we did statistical analysis, adjusting for the changes in weight and the change in fat mass and change in waist circumference, all of those. And the effect, the differential effect of the diets on insulin sensitivity wasn't really affected. That's partly also because we saw similar changes in insulin sensitivity, these similar declines in insulin sensitivity in the dairy groups, but weight really changed substantially only in the full fat dairy group. And so, what we concluded there is that, yes, calorie intake and weight actually did increase in the full fat dairy group, and that, by itself, I'd say, is a concern. But that is likely not been sufficient to explain the increase in insulin resistance in both of the dairy groups. So these are independent effects, and it's certainly, as you said, possible that the increase in insulin resistance by itself is a concern, in that it could increase the risk of diabetes in the long term. We'll get to that later, I have another hypothesis that I'd like to share when we're done with some other endpoints here.

DANNY LENNON: For sure, no, super fascinating, and just as you were speaking, I pulled up some of the results that you mentioned there. So just four people in that situation where we're comparing intakes

from that five-day controlled feeding period, during that wash-in period where we have this dairy limit, if we compare that then to the three conditions and the controlled feeding periods there, those that continued on the limited dairy diet we see remaining stable in terms of caloric intake, the low fat dairy diet saw an increase of 166 calories per day, plus or minus, 267; and then the full fat dairy diet was 384 calories per day, plus or minus, 175 – so as you noted, a considerable increase in calories that weren't compensated for in that full fat dairy diet. And one of the interesting things was you were also able to compare those controlled feeding periods to the 24-hour dietary recalls, and that seemed to kind of corroborate things quite nicely. Right?

MARIO KRATZ: Yeah, which we were happy with, I mean, the 24-hour recalls are certainly not the best measure of energy intake. They give you a good sense of otherwise the habitual diet of people, but they're not fantastic for estimating total energy intake.

DANNY LENNON: So before we start wrapping up some of the conclusions from this, whether it was anything else that either took you by surprise or was certainly noteworthy, or that generated some discussion between you and your coauthors, after the results came in?

MARIO KRATZ: Yeah, I mean, we were all surprised how null the glucose tolerance data were, the fact that it didn't matter at all, whether you consume dairy or not, and whether the dairy was full fat or low fat with regard to glucose tolerance. I think, partly, it's a bit disappointing in that you always feel like if you had an additional weapon with which to improve your metabolic health, that would be a good thing. Right? So if you knew, for example, that either staying away from dairy or consuming a certain type of dairy would improve your glucose tolerance, that would be nice; but at the same time, I think it's also somewhat reassuring, in that, it shows again how flexible our bodies are, and that the

body functions extremely well on a variety of different diets. And dairy, in this case, seems to be optional for people if you want to enjoy dairy. With regard to glucose tolerance, it's probably fine. Whether the small increase in insulin resistance is a concern, I think it's unclear at this point, but remember, this was basically people eating quite a bit of full fat dairy, in this kind of controlled setting for 12 weeks, whether now you, if you eat some cheese and have some milk once in a while, if you see similar effects, and whether that's a concern, and that it relates to an increased risk of type 2 diabetes, I think we can't answer from the study.

We always try to jump to some conclusion to make our paper more sexy, and sell it, right, to make it seem like this is a huge deal; but the reality is, we really don't know yet whether that's really a concern. The effect size was fairly small, right? So the increase in insulin resistance wasn't huge. And there is another potential explanation that could actually explain this.

DANNY LENNON: So with that, before we maybe draw general conclusions, we might actually be able to get into the second paper where we're looking at some other outcomes. And so, for people listening, we essentially have the same diet setup that we have, and the same dietary groups that we've just already mentioned, but this time in the second paper, the outcomes you were looking at was the fasting lipid profile and blood pressure. First of all, again, what was the kind of thinking behind looking at these specifically, of course, there's some obvious reasons for doing so, but what was the thought into going in and looking at these outcomes, specifically?

MARIO KRATZ: So I over just reading literature over the years, I'd gotten very interested in dairy fat, in that, dairy fat is, I think, the most complex fat humans eat; in that, there's like 400 different fatty acids in there, and many of them are

derived from the fermentation of grass and grains these days in the cows' very complex gastrointestinal tract. And so, we often like to think about dairy fat as just this fast rich and saturated fats or fatty acids. But that's only partly true, because there's actually a lot of really interesting short chain branched chain fatty acids in dairy that may well have very different actions. On top of that, most studies that I was aware of that had tested dairy fat, as it relates to specifically blood lipids, you know, cholesterol levels and so forth, had tasted butter and isolated dairy fat. And I was interested in what if people consumed the dairy fat, not in the form of butter, which really, I think, even though, as an Irish, you may be taking issue with what I'm saying here, no one in nutrition community really recommends eating butter by the stick.

DANNY LENNON: Right.

MARIO KRATZ: I'm not entirely sure we need to keep testing butter, right, because the reality is, even if we don't see a huge effect with butter, we're not going to recommend people eat huge amounts of butter. But if people ate dairy fat in the form of intact whole complex foods, like milk, yogurt and cheese, would we similarly see negative effects on serum lipids? And so, yeah, we were just really interested in this topic, and so, even though this was kind of an exploratory endpoint, we included a very sophisticated measure that's not often included in these types of trials, in that, we measured in normal lab tests, the total cholesterol, the HDL cholesterol, the LDL cholesterol, and triglycerides, the free fatty acids, but we also basically took an entire large vial of plasma, and basically divvied up all the lipoproteins floating around in the blood into 38 fractions. And I'm not sure if you've seen this before, Danny, it's not done often, because it's fairly expensive. But basically, what happens then, if you fractionate them by density, you'll get a whole bunch of fractions that we commonly refer to as very low density lipoproteins; then

you get a whole bunch of fractions that we refer to as ideal or intermediate density lipoprotein; then we get a few fractions that we refer to as LDL or low density lipoprotein; and we get a few fractions that we commonly refer to as HDL, high density lipoprotein. And so, all of these carry different fats around the body, including cholesterol, and commonly, we just measure the cholesterol content in these.

Now, by looking at all these different individual fractions, we can really see if there's a change with any intervention that, for example, leads to an increase in LDL cholesterol. Where does that change occur? Does it occur in the more small, dense LDL fraction that we know is more strongly associated with cardiovascular disease? Or does it occur in the more large point LDL fraction that's only weakly, if at all, associated with cardiovascular disease? And we can see similar changes in other, much more finer fractions of the other lipoprotein classes. And so, basically, we wanted to make sure that if there's an effect of these full fat dairy diet, specifically, that we wouldn't miss it, and that we'd really understand deeply, like, what's really going on here, and is this likely to increase cardiovascular disease risk.

DANNY LENNON: I was going to say you're certainly not alone in being intrigued by dairy fat and cardiovascular disease in these outcomes, because even discussing cardiovascular disease, saturated fat on the podcast before, one of the interesting thought processes or questions that listeners often have is, well, what's the deal with dairy, it seems very clear on things, like, like you say, high consumption of butter in isolation or fatty cuts of meat and so on. But then we start to see a slightly different picture when we look at dairy in terms of from cheeses and yogurts, and so on. So I think the interest in that question is something many people share. And like you said, there's a lot of interest to explore within this particular study. So from where we are now, that gives a good sense of the aims here,

what's the kind of next step about going about this particular set of results and methodology?

MARIO KRATZ: So with regard to serum lipids, basically, what we were even struck with is we totally, again, got a null result; and I think in this case, this is really an interesting null result, in that, there was not a single measure, you know, total cholesterol, LDL cholesterol, HDL, triglycerides, or any of these fractions of these 38 fractionated lipoproteins in which we measured the cholesterol content, there was not a single measure that differed between the three intervention groups. So again, in other words, your serum lipid profile is not affected even a little bit. I mean, if you look at some of these curves, they're basically lying on top of each other. Right? It's not affected even a little bit, independent of whether you eat dairy versus no dairy, and whether the dairy is full fat dairy or low fat dairy. And so, really, I think the compelling conclusion here is that the effect of dairy fat on the serum lipid profile is very different, whether the dairy effect comes from isolated source like butter, as opposed to, if it comes from a complex dairy food, like yogurt, cheese, and milk. And I think that's encouraging, in that, it again leaves us as a consumer more freedom to choose, and not maybe be as overly concerned. At the same time, I will say, I've been interviewed a lot about this work, and the one thing that frustrates me, is almost always do interviewers ask me about things like, I'm not sure if I can mention the brand, but the kind of coffee where you actually add butter and other fats to it. It's probably the number one question I've gotten to all of this work about dairy, I'm not kidding. And I keep emphasizing that all of the work, including in our summary of observational studies, suggests that consuming full fat dairy in the form of the whole foods, whole milk, full fat yogurt, full fat cheese does not seem to have any of the negative effects that we would anticipate, say, with regard to serum lipids. But that does not mean that we can eat as much butter, cream and ice cream as

we want and hope that that's going to be similarly neutral or beneficial to us. So I think these are two different totally different things.

DANNY LENNON: Yeah, and I think, yeah, the point you make is so important that when we're thinking about this as a result, it's an important one from this perspective of when we start translating this from nutrients to actual food based recommendations for people at a broad scale. Now, we're actually thinking about, well, what foods do people consume, and then what are the implications of eating those types of foods; and now we have a good base to say, well, there is going to be a difference between whether you're getting that source with this nutrient from food, extra food, why, as we've outlined here. So maybe to, before we finish up, to dive into this, a small bit more, just to give people a context, of course, the full fat dairy group is going to be consuming more total fat and more saturated fat relative to the other groups presumably, because they're the foods they're adding in – in terms of the quantification of that, do we know what the changes in people's nutrient intake look like in terms of before the trial and then going into the trial, and even between groups, the differences in, say, the level of saturated fat between them?

MARIO KRATZ: Yeah, so I think we have that on the paper, and I don't know these numbers in my head, I'm glad to say, but saturated fat certainly went up, as we would expect, right, quite substantially in the full fat dairy group, I think we have a sentence in there somewhere that, what we administered included 0% dairy fat in the limited dairy arm 8 grams per day in the low fat dairy arm. And I do think it's 29 grams of dairy fat in the full fat dairy. And you can roughly estimate about half of that is saturated fat from dairy. So it's not a huge amount, but it's also not nothing. Right? It's certainly the normal amount that people would eat if they normally consumed full fat dairy foods. And not seeing basically any effect there on the serum lipids, I find, as you say, even though it's

a null result, I think it's an important null result.

DANNY LENNON: One other thing that people may ask them about is if we do see an increase in saturated fat intake within, particularly the full fat dairy group, and if we're thinking about the, number one, the magnitude of the change, and the time course of that change, is it possible then that, let's say, there's a certain threshold of total saturated fat intake that they didn't get beyond, and therefore, there wasn't the same deleterious changes that if we added even more dairy, full fat dairy, so we went to six servings a day, for example, that you would start to see that, or, do you think there is actually something within these various, I suppose, the food matrix that that occurs within dairy foods that may be actually protective, what's the best kind of reasoning we have right now as to why dairy fat seems to have this differential impact relative to other sources of saturated fat?

MARIO KRATZ: Yeah, good question. Let me correct myself first, because I just said, dairy fat has 50% saturated fat, that's not correct. Dairy fat has more saturated fat, it's 40 to 50% of the long chain saturated fatty acids that have been linked to increase in cholesterol levels. The others are short chain fatty acids that we're not usually as much concerned about; or other, like, branched chain fatty acids, they're also saturated, but they don't share the same effect on cholesterol levels. So actually, that could be one reason why dairy fat consumed like this, you know, even though dairy fat is a lot of saturated fat, not all of the saturated fat in dairy is of concern with regard to serum lipids, we know that fairly certainly. The other is, there's certainly the possibility that dose effect plays a role here. We cannot answer that. I can only speculate. I would guess, yes, that if you consumed it more and more and more, you're going to see an effect on serum lipids at some point. I don't think we can rule that out based on these results, but I also wonder to which degree then is it relevant for the general public.

We pick three servings a day, because what we actually even found in the study is that that's the amount most people want to eat. It's not like most people would eat six servings a day regularly every day now. And the food matrix question though, I think, is a really interesting one; and that's something we're just now starting to understand that if you consume dairy like this, and you have, for example, cheese that's extremely rich in calcium, could some of that fat, for example, be bound to calcium and lose some of its negative health impacts. And there's a whole bunch of other factors that have been hypothesized as playing a role in this. So I do think we don't fully understand yet how the food matrix and which components of the food matrix are at play here, but it's very likely that that's really one benefit that we're reaping, if we're consuming foods in their more intact whole food form is that we're getting the getting a package of nutrients and other components that, in many times, interact in ways that could be beneficial to us.

DANNY LENNON: Fantastic. There's so many little things that we could spend a long time talking about, but that that may be for another day. So before we sign off here, Mario, what are maybe some final conclusions or the big key ideas that you would want listeners to take away from this discussion, and from the work that you've done in this particular area, what are the main things for them to keep in mind?

MARIO KRATZ: Maybe two things, so one is, I think I should get go back to the whole increase in insulin resistance, because that's maybe one thing that many listeners will be worried about after hearing this. And there's one other thing I wanted to add to this, and that is, as I mentioned earlier, we had measured in our trial, all the major determinants of insulin resistance as we know them, body weight, fat mass, but also liver fat content and measured the inflammation. And we, for liver fat and measured inflammation, we also didn't see any differential effects of the diets. So given that

the insulin resistant inducing effect of diet switch in dairy was basically preserved after adjusting for changes in body weight or fat mass. What puzzled us is that we don't really understand why insulin resistance increased in the two dairy arms. All the major determinants of insulin resistance didn't really explain it, and so, one thought here is that dairy is known to be very, what we call, insulinotropic, like, it triggers a strong insulin release.

So if you consume a glass of milk, for example, you get a certain fairly small increase in glucose levels, but you get a fairly substantial increase in insulin, way bigger than what you would expect, given the small rise in glucose. And that's thought to be because dairy is one of the few foods that actually has some sugar in it, but also some protein, some amino acids that trigger insulin release. And so, when we think about how this would play out in a study like this, where people consume dairy foods three times a day with their meals, is that you would expect the dairy to actually acutely trigger an increase in insulin, right, because it triggers these insulin increases. And the body, in this case, would have to basically reduce its sensitivity to insulin, in order to not become hypoglycemic. Right? Because these were not people with diabetes.

So, high insulin levels would be expected to be countered by a compensatory increase in insulin resistance. And that's actually been known, like, if you do the so-called clamp experiment where you experimentally increase insulin levels, within just 24 hours people become massively insulin resistant. And so, it's possible that basically on a diet rich in dairy, we're just finding a new equilibrium of higher insulin levels throughout the day, triggered partly by the dairy foods that we're consuming, and a slightly increased level of insulin resistance. And I've discussed this with a number of endocrinologists and diabetes researchers, and I think we're not, all of us, we're not sure whether that's really a bad thing,

whether that would really in the long term, increase our risk of diabetes, simply because we're just finding a new equilibrium. So that makes sense? It's a bit of complex concept, but I think it's important to understand, in that, we shouldn't take the results from this trial, and pour down the drain all of our dairy foods now because we're concerned about that insulin resistance. So I'll say this again, the increase in insulin resistance was small. We're really not sure yet whether it will be associated with an increase in type 2 diabetes in the long term. I'd say all the observational studies that are out there do not suggest that it would, simply because it's really – I cannot think of a single observational study in which people that consume the most dairy have an increased risk of type 2 diabetes. And observational studies, I'll be the first to tell you, have a lot of issues. But I think if you have dozens of observational studies, and none has ever even suggested, there could be a positive association, I think, that's somewhat reassuring.

So personally, I will therefore conclude, personally, I'm not too concerned about that insulin resistance increase for these reasons. But I'm a little bit concerned about, as a takeaway, is the increase in total calorie intake and the body weight and the full fat dairy arm, and I will disclose maybe just that's going to be interesting for readers, I've switched from full fat milk and yogurt to lower fat versions. Personally, for me and my family, I do think there's a potential there for that to have negative consequences in the long run. Other than that, it seems to me with regard to all of the endpoints that we measured, be it serum lipids, be it liver fat content, which is really an endpoint that we're going to be much more focused on in the future, I feel like what our data show is it doesn't seem to matter all that much, whether or not you eat dairy, and whether or not the dairy or full fat or low fat, I'd say, in total, our data do suggest maybe slight preference to lower fat versions, if you have access to them, mostly for this bodyweight

relation, and basically, to try to not trigger an excess calorie intake. But other than that, mostly just enjoy whatever you enjoy, right? If you don't like dairy, stay away from it, you're probably fine. And if you do enjoy it, again, I'd say, it's in my mind actually reassuring how little it did seem to matter with regard to most endpoints.

DANNY LENNON: Yeah. No, I think that's an excellent and very fair and reasonable conclusion. I think what also fits together from what you've just said there is given that, yes, there was this slightly adverse result in relation to insulin resistance, however, given that there was no change in any of the other related markers that we didn't detect anything there, plus we don't see anything from the observational literature that would even lend more support to this hypothesis you've put forth of maybe this is essentially an adaptive process. Right? It's more of a transient insulin resistant as opposed to a pathological insulin resistance. And we know in other cases, that tends to happen, not the exact same, but, for example, if someone adopts a ketogenic diet, we know that there tends to create a degree of insulin resistance, but not in the same way as we would think of pathological insulin resistance that leads to problems. So I think that all fits together nicely, and it was really well explained.

MARIO KRATZ: Actually, if I may add to this, if someone goes on a low carb diet, we know for sure they become glucose intolerant to some degree.

DANNY LENNON: Yes.

MARIO KRATZ: I mean, there's actually quite a bit of literature on this, that if you have a high fat intake, low carb intake, you become less glucose tolerant. That similarly, I would argue, isn't all that concerning, because you don't need to be as glucose tolerant if you don't consume carbs. So these are these types of adaptive responses the body makes that make a lot of sense, and that if we are looking at this superficially, we may

make a big deal out of this. Right? In this case, many people could get outraged, so what, glucose tolerance gets worse with low carb diets – that's a major minus for low carb diets. And I argue it isn't, because the body doesn't need to be extremely glucose tolerant in this setting. And if you change from your low carb to a more mixed or even high carb diet, it would revert itself by itself spontaneously within a few days. So I totally agree with you, I think the results need to be interpreted, looking at the bigger picture here, and there's nothing really in the literature anywhere or even as a plausible mechanism that would make me overly concerned about this increase in insulin resistance.

DANNY LENNON: Fantastic. So before we get to the very final question, Mario, for people who are looking to find your work or find you on social media or the internet or anything like that, where are the best places you would like to send them?

MARIO KRATZ: So, well, currently nowhere in reality, because my lab is close, I still have a website, so if anyone wants to go there, look at my work, even though the website hasn't been updated recently with these papers. That's at fredhutch.org, you can look for Kratz Lab, there's my websites still there with all of my dear coworkers that I enjoyed very much working with. By the way, before I forget this, I should really mention Kelsey Schmidt, who was the doctoral student whose dissertation work this was that we talked about. By no means, do I want to give anyone the impression that I did this year. If you look at the papers, there's a lot of authors on this. And actually, other than coming up with the idea and writing up the study protocol, I probably did the least amount of work. So definitely worth the disclaimer here. With regard to my new business, I do have a business, I have a website, but there's nothing on there yet, it's going to be called Nourished by Science, where the idea really is to provide evidence based information. Feel free to, depending on when you post this

podcast, there may be some content up, I'm hoping to launch this fall. And basically, just sharing this type of more in-depth information, showing really the complexity of the science, but also really the evidence behind it, and without wanting to sell a book or some product or supplement or something, and spinning the science accordingly. That's really kind of, hopefully, what I'm hoping to achieve with this.

DANNY LENNON: Fantastic. I very much look forward to consuming that content as it comes out into the future. So with that, we come to the final question I always end the podcast on, and this could be to do with anything, even outside of today's topic, and it's simply: if you could advise people to do one thing each day that would have a positive impact on any area of their life, what might that one thing be?

MARIO KRATZ: As a nutritionist, I probably should pick something with nutrition, but I'm going to say, meditate. I will say that I have now meditated for a few years, and I just do it for 10-15 minutes every day; but it's probably the number one thing, I would say, contributes to my overall wellbeing and hopefully the wellbeing around me. I think of people around me, I think, it's overall really wonderful practice to get into even though it's hard to kind of get started. But I've even considered, if I could start this over again, as much as I believe in nutrition, I think meditation teacher would have been a good career for me, like, I'm really convinced that that's a major benefit to humankind.

DANNY LENNON: Amazing. Is there a particular type of practice or way you like doing it, how would you recommend people might get started?

MARIO KRATZ: Yeah, I follow Insight Meditation. The way this is taught by Jack Kornfield, for example, the teacher I really like. And I really, really, to be honest, I'm not an advanced practitioner, I don't do anything fancy or anything. I have an app, I do 15 minutes every day, right in the

morning after dropping off my kids. And I really barely ever miss it, like, it's really become a habit that I really treasure, and I'd encourage listeners, if you have any way of trying to find a way to tag this on to something else, that's really a great tip I've gotten from Atomic Habits by James Clear. Like, you've got to do something where say you brush your teeth, and then you do it; or, you bring your kids to school, and then you come home and you do it, where you tag it on to something you already have to do every day or you do every day. Try to make it a habit to basically tag on 10 minutes of meditation practice every day, and I think you'll be very glad you did. I certainly am, and I actually don't know anyone who's ever told me they've meditated for years, and they still regret or they wasted time. I've never heard anyone say this. It's really one of the things that universally people appreciate once they do it.

DANNY LENNON: Yeah, it's one of those things that, as you say, if someone has done it for, beyond that kind of threshold of where it's difficult to make it a habit once it's established, I am yet to meet someone who says oh yeah, I wish I'd never started it. Dr. Mario Kratz, thank you so much for this. This has been really, really a pleasure to talk through this with you. I very much appreciate it. I very much appreciate your contributions and for taking all this time to talk to me tonight. It's been an absolute pleasure.

MARIO KRATZ: Yeah, thank you very much, Danny, and thank you for everything you do for the nutrition community with the work that you're doing. And let me add, I understand some of this was maybe fairly complex, so if anyone wants to email me, I'd be happy to correspond with you guys. You'd probably find me on Twitter with my name as well or through my website that I mentioned earlier, nourishedbyscience.com. There's a contact form you can send me an email.

DANNY LENNON: Fantastic. Thank you so much. Really appreciate it.