DANNY LENNON: Sarah, thank you so much for joining me on the podcast today. Very much appreciate it.

SARAH BERRY: Pleasure. Thank you, Danny, for having me here today.

DANNY LENNON: Can you maybe just outline to people listening a bit about your background, your work in academia, your research interests, anything else that may be relevant?

SARAH BERRY: Yes, Danny. So I'm a nutritional scientist. I have had now about 22 years experiences as a nutritionist. I originally discov -- studied physiology at Sheffield University. And found I was really fascinated by the human functioning in terms of how nutrition impacts how we function. So I then went on to do a Master's in nutrition and a PhD in nutrition, and my passion and my interest just built on from there. And I find the work that I do fun. I love finding out more each day about how we respond to food, how complicated we are, how complicated our responses are to food. And at King's College London, where I'm an academic, I lead many randomized control trials, looking at the effects of different diets, and particularly different fats, and how they impact our cardiovascular health. And this really led me into the world personalized nutrition, as we

started to see over the last 5-10 years, just how much disagreement there were between studies and how different people's responses were, even within my interventions, which are incredibly tightly controlled, and how variable everyone was to the same given intervention. And so the last three years, I've been involved together with a startup tech company called ZOE, in the PREDICT program of research, which is the largest personalized nutrition program research and a really exciting, really broad program of research as well, which is really exciting to be a part of.

DANNY LENNON: Yeah, and I definitely want to dig into some of the details related to PREDICT. But maybe before getting into that body of work, you just mentioned there that you obviously have a lot of expertise related to dietary fat and looking at that role in cardiovascular risk, for example, and something that we'll probably touch on again later relates to the postprandial lipemia that results after consuming a meal and the role of dietary fats there. Can you maybe just explain for people what we actually mean by postprandial lipemia, and anything -- and how that kind of relates to a bigger picture of chronic disease risk, and particularly cardiovascular disease risk?

SARAH BERRY: Certainly. So if we take a step back a little bit to think about how typically we would look at responses to diets or medicines, we would typically look at a baseline level. So many of us if we're asked to go to the doctor to have bloods done, we're told, “Can you come fasting?” So don't have any breakfast. We want to look at your fasting levels. And this is how typically, and historically, we've measured responsiveness to diet. So we would put someone on a diet for intervention, you know, where we might change a particular aspect of their diet. Two months later, they come back, we have them fasted, and we do a fasting blood sample.

But we're starting to understand that actually, that only tells us a really small snapshot of what's going on. And when we consume meals, we have something called a postprandial response. So we consume meals that contain mixed nutrients. So they contain carbohydrates, fats, protein. What happens is, is as you consume that meal, you release the fat as triglycerides, and you release the carbohydrate, typically, it's glucose into your blood. And this causes what we call a postprandial metabolic response, postprandial just meaning post-eating. And so when you consume any meal that contains fat, you have an increase in blood triglycerides from the fat. And this increases over about an eight hour period. So it reaches a peak about four hours and returns to baseline around eight hours. And for glucose, something similar happens, but it's a lot quicker. So the carbohydrate in the meal causes an increase up to about 30 minutes, and then it returns to baseline.

Now, if we think of how we typically as individuals eat and how our dietary patterns are, we consume multiple meals, don't we, throughout the day. We don't just consume one meal. So if we think about consuming, typically three meals, breakfast, lunch, and dinner, and two snacks, which is the average eating pattern in the UK, and in many populations. And if we were to actually map those responses that I just described, so if we were to think of each one of those eating events, we have this short, sharp rise in glucose. So imagine this kind of little short kind of blip in glucose. And then we also have this more prolonged rise in triglycerides from the fat in the meal. What actually happens if we have that at each of these eating events that I've described, you actually spend about 18 hours of the day in this postprandial state. So you're actually only spending a really short period of time in this fast instant.

So we now know that it's really important that we actually start to look at the postprandial responses to food, and not just the fasting

responses. And one of the reasons for this is that many of the postprandial responses to food, actually underpinning these chronic effects is long-term effects. So how we acutely in this postprandial period respond to a given nutrient or food is what often goes on to cause these long-term effects.

And so if I could use lipemia, like you said, as an example, so we have this rise in blood fat. Okay. We have this rise in blood triglycerides after we've consumed a fatty meal. We, like I said, it's peaking to four hours, returning to baseline to eight hours. During this eight hour period, you're in this really in this real kind of state of metabolic flux. So what's happening is, is that you're having a whole host of downstream events that are occurring, and that these go on to -- to impact our health. So we have what's called lipoprotein remodeling. So we have change in the composition in the size of lipoproteins, which are these very specialized particles that transfer fat around our blood. And so what happens is if you have a very elevated and prolonged postprandial lipemic response, so prolonged increases in triglycerides, you actually have the generation of quite harmful lipoproteins. So you have them to -- they are remodeled into kind of bad lipoproteins. So you instead of having lovely large particles, which we know are good for us, we get these small ones which aren't so good for us. We also get very small LDL particles, which aren't good for us.

Additionally, it also initiates a cascade of events that results in the release of inflammatory measures. So you have increase in inflammatory cytokines, for example. And we can actually see this directly impact the functioning of our blood vessels. So what we can see is, after you have a meal about four to six hours after you have a high fat meal, you can actually see an impairment in how our blood vessels function. And we do this in our own studies using a quite specialized technique using flow mediated dilation. And it also

impacts a whole host of other factors. So hemostatic factors involved in blood clotting, for example, oxidative factors as well. And we now know from really large epidemiological studies that postprandial lipemia, so triglycerides in the postprandial state is actually a better predictor of cardiovascular disease than looking at these traditional lipid measures such as cholesterol. And so it's really highly relevant to be looking in the postprandial state in terms of lipids, but also in terms of glucose, this we've known for a long time as well, because of the link of postprandial Glycemia with obesity, type II diabetes, insulin sensitivity, etc.

DANNY LENNON: Yeah. I think that's a beautiful explanation. I think that sets the stage well, for us talking about personalized nutrition, because essentially, it's not the fact that there's an elevation in either triglycerides, fatty acids, glucose, but it's the actual response and that over a period of time that you just mentioned, I think you alluded to hyperglycemia, we see a similar issue there, presumably, where it's not the fact that after a meal, glucose in the blood elevates, that's necessarily a problem. It's what is an individual's response to that? How does it come back down? How long does it stay elevated? And we're seeing differences between people there. So presumably, that's what we need to focus on in terms of individual risk relates to not does a certain substrate cause an increase in these blood markers. But what does that response look like?

SARAH BERRY: Definitely. I think you've hit on a few really important points that I'd like to pick up on. So one is the shape of the curve. So you mentioned about, you know, how quick it goes up, and how quick it goes down. So, typically, we measure, we use a single measure when we're looking at a glycemic response to a food. And we measure something called the two-hour area under the curve when we measure. That just gives us a food response. But actually, what we know is, is the subtleties that’s so

important. And this is the case for so much so many different aspects related to nutritional research, as we're, you know, evolving our knowledge and nutritional research, we're realizing is those subtleties. And so what we're trying to do with the research PREDICT, and also my other studies, is really unravel what part of the curve? Is it that you want to actually belong the overall response? Is it just that you want your response to come down more quickly whether it be it triglycerides, glucose, or other metabolites? What is it that we want to actually modulate, to have the beneficial downstream effects?

And I think another point that you mentioned, that's really important to note is that having an increase in glucose, in triglycerides, or even inflammatory measures itself isn't bad. This is normal metabolic processing, you know, we don't want everyone to have no response. Otherwise, we can't eat anything, you know, it's a normal metabolic response to consuming food, it's to have a rise in glucose, a rise in triglycerides, a rise in inflammatory measures. What we don't want to do though is we don't want to have repeated excursions that stay elevated for long periods of time, in the case of triglycerides, or in the case of glucose, it becomes so high that the counter regulatory system of insulin pushes it so low, that you then have this crash, that, you know, is associated with hunger, eating more, you know, subsequent meals, etc. So it's really about thinking about, you know, how we can modulate an individual's responses, you said, to make a healthier response?

DANNY LENNON: Yeah. And I think, typically, we've seen in nutritional science, looking at certain foods and predicting what is the response after we eat that, people will be familiar with things like the Glycemic Index, for example, which is a simplified way of looking at one of those markers in an isolated food. But this discussion, what I suppose PREDICT is really trying to get to is that even if we control for a

specific type of food, we don't know what the exact response is going to be in a given individual, and that the response can be much more different than we would even potentially imagine. Can you maybe give people an idea of what that interindividual variants can be like in types of some of these responses?

SARAH BERRY: I think it's important we think of before we talk about interindividual variation in responses, we think about what we typically looked at in nutritional research. So like you said, typically, we will measure a group of individuals' response to a given food and what we would typically publish and many listeners will be reading these kinds of articles that we, myself as a nutritional scientist and other nutritional scientists have published other mean responses. So we would typically say, okay, Danny, you and 100 other people are going to go on, you know, a high fat diet and then we've got another 100 people that are going to go on a high carb diet. Let's look at how you differ. And let's look at what's more effective for a given outcome. And we would typically show the mean. So does your group, does Danny's group who are on the high fat diet differ to the other group that are on the high carb diet?

Quite often, we might not find a difference. But if you delve deeper into the data, you see huge variability how each individual responds. So the headline of that, in terms of what's published in the actual journal would be no mean differences in high carb or high fat diet. But actually, if we look at individual differences, you will see some people that hugely benefit from the high carb, but other hugely benefit from that the high fat and vice versa. And one of my collaborators, Christopher Gardner at Stanford University did a study just like I've described. It's called the DIETFITS study. And again, they found no difference between a six week high fat, six week or a high carb diet, but they found this huge variability. So for some people, one was the best way and for other people, the other diet

was the best way. And we also see this in postprandial responses where we see more than a 20-fold difference in how people respond to the same food.

So the kind of studies I've run for the last 20 years are very tightly controlled randomized control trials, where I will recruit a very narrow phenotype of people. So I will recruit just men, for example, in a narrow age range with a very tight inclusion criteria. I will control everything for 24 hours before that, we know affects postprandial responses. So no exercise, no caffeine, no alcohol, consume a standardized meal, arrive at this time in the morning. So everyone is standardized yet, and then I will give a standardized test meal containing a standardized amount of fat, protein, carbohydrate. So despite all of this being standardized, and despite really tightly controlled clinical conditions, again, I will still see this 20 fold difference, where one person will have this huge elevation. And then this other person will have a really low response.

Now when I write this up, because I might compare one fat one week to another fat another week in the same room, I'm only typically showing this is how this fat differs to that fat. I'm not showing genuinely how, you know, we have this 20 fold difference. But we know now that actually this is what we really need to be unraveling in nutritional research. But that itself, it's very challenging. And we can also discuss that that, you know, before we've not been able to do that. But now we're at this real juncture where we can actually, you know, unravel personalized responses, what's causing it, why?

DANNY LENNON: I suppose that's the exciting thing. And where a lot of the stuff with PREDICT comes in that we're at a point in time due to technology and the ability to integrate machine learning and the ability to deal with huge amounts of data that before we're just not possible. It -- we can actually look at these interesting things. And

so, as we've mentioned PREDICT a few times, can you maybe give people an overview of what this project essentially is, some of the kind of sub studies that are falling with -- within under that and then afterwards, maybe we can jump into some of the specific studies itself?

SARAH BERRY: PREDICT is a program of research that was born out to a growing understanding that there is no such thing as a one size fits all approach to diet that we all respond differently. And it really capitalizes on the exciting times that we find ourselves in nutritional research. So we're really at this exciting time that we can capitalize on novel technologies to measure high resolution people's responses, as well as using AI. So machine learning to actually in a meaningful way use the kind of millions of data points that come out of all of these novel technologies. And the purpose of PREDICT was to take advantage of all of these new opportunities in nutritional research. So multi-omics, genetics, metagenomics, etc. And to really unravel how so the size of the power people different, what's causing these differences. And then to look at whether we can use AI and machine learning to predict these differences.

And there's a whole series of studies within PREDICT. The first one is PREDICT-1, which is was recently published in Nature medicine. And since then, we followed on a refined and developed a whole series of studies. And the aim of PREDICT-1 was to, firstly, assess how much variability there is in postprandial responses to food. And then look at what's the main determinants of these differences? Is it how we saw it at the time of days exercise? Is it how much sleep we've had? Is it what we're eating? So is it the composition of the meal? Is another factor such as is it our microbiome? Or is it our genetics? Or is it our blood biochemistry? And integrate all of these measures and omics and then use a machine learning model in order to predict.

And a big part of the PREDICT-1 study was remote testing. And this is, again, another really exciting time that we're in in nutritional research that there's lots of possibilities now to remote test. So we don't have to have everyone coming into the clinic in the way that we traditionally have in nutritional research. We have wearable devices. We have continuous glucose monitors. We have activity monitors. We can do dried blood spots measurements at home for measurements of triglycerides, insulin and C-peptide, for example. And, you know, people can collect their install sample and send that off. So then we can capitalize on citizen science as well, people's interest to find out more about themselves. And this is what we've really done with our ongoing PREDICT trials that PREDICT-1 was quite intense. It did involve a clinic day and then an at home period. But our corresponding PREDICT trials where we're delving a lot deeper into understanding and unraveling how we respond to food and what determines these responses. And maybe doing all of these studies exclusively remotely.

DANNY LENNON: With the at home or the ability to people to do this remotely, is that you obviously have that benefit of people being able to stay in their normal kind of free living conditions. And we always like to talk about like external validity being great in that, in that sense, but then we typically then lose some of the ability to get some accurate measures. But as you mentioned, now we're in a place where actually we can get people to get measurements of this data pretty reliably from their, their home. So it's like a nice balance of both that maybe in the past hasn't been, been possible to do.

SARAH BERRY: Definitely. I think an example I always use, I think for nutritionist really hits home is traditionally we've relied on very high scale, but low resolution data. So if we are thinking of dietary assessment, this would be food frequency questionnaires. So we can have these massive studies like the Nurses' Health Study

that provides a state on dietary intake, using FFQs, but it's very low resolution state blood. It gives us a very murky picture. All what we've been able to do is conduct a high resolution studies, but very low sample numbers. So a kind of clinical randomized control trials. And the equivalent from the FFQ for the dietary assessment would be duplicate diet records or weight diet records. Really cumbersome, but they give us that really clear picture. So we've either had the option of either or now you hit the nail on the head, we have the option that we don't have to make a choice between either or what we can do is collect high quality, high resolution data at the scale, traditionally, we couldn't meet all of these new technologies.

DANNY LENNON: With PREDICT-1 obviously, for people listening, we will link up to the published paper in the show notes for this episode, which I encourage you to check out for all the details. We can only really scratched the surface of some of the methodology here. But related to that if we talk about just some of the brief things that people may need to know about the methodology, and particularly, I think one thing might be interesting related to the participants used. I know a large part of the cohort was made up by people from the TwinsUK registry. For maybe people who have -- who are unfamiliar with that, can you mention why that is significant and just what it is?

SARAH BERRY: For the PREDICT-1 study, we capitalized on the TwinsUK cohort, which is a cohort, the world's largest cohort of twins. It's led by Professor Tim Spector, who's actually also the lead scientist on the PREDICT program of research. And it's a really unique resource because it allows us to differentiate between genetic influences within PREDICT more of our response to food versus all of the other influences. As a cohort, it's a really valuable cohort. It's a longitudinal cohort. So these twins have been studied for many years at four yearly intervals where they have a whole host of

measurements from dietary assessment to vascular measurements, a whole host of blood measurements, etc. So it's a very rich source.

Now, we capitalized on them so that we could unravel the various determinants, like I say, and, and look at how much of people's responses to food are due to genetics versus other factors. And they formed about 65% of all PREDICT-1 cohort in the UK. We also and this is out of the 1,000 people in the UK. We also had 100 people in the cohort in the US, which was our validation cohort, which for machine learning is really important to have a validation cohort from which to test our prediction algorithms.

DANNY LENNON: So can you maybe and you've alluded some of it, but can you maybe remind people what exactly what type of data was being collected within PREDICT-1, how that was done, and then maybe some of the, the findings from that?

SARAH BERRY: So it was a two week study. Our participants attended our clinic at St. Thomas's hospital, or MGH for our US participants for one of our standardized postprandial test study days, very typical to the study days that I've been doing the last 20 years at King's. So these people arriving fasting. They have a whole series of measurements for us to look at their anthropometric. So they would have this whole fat measured using DXA, BMI, body weight, waist circumference, etc. We would do other baseline measures such as blood pressure, heart rate. They would complete quite in depth questionnaires on frequency, lifestyle, medical questionnaire. They provide us with a baseline stool sample for metagenomics. So we have all of that baseline data. They would then have fasting blood sample collected, and we would then give them one of our standardized test meals. And these test meals consists of muffins. And these are what I've been using over the last 20 years for my research at King's, because they're the best way for us to deliver a very

controlled amount of nutrients in one single meal where we don't have the complexity of the food matrix so that we can really, we can adjust them from day to day, without any other complex effects that you would typically get with other kind of food sources of matrix.

So they would have a test meal in the morning, and they would have another test meal at four hours. So typical of a typical breakfast and lunch eating pattern. And we would collect blood samples at sequential intervals about every 15 minutes for the first few hours, and then about every half an hour up to six hours. And these blood samples will be analyzed for a whole host of blood essays for the typical clinical measures such as triglycerides, glucose, but also for metabolomics so that we could really do a deep dive into what's actually happening and changing postprandially.

When they finish their clinic day, they then started a 13 day at home phase. And this is really exciting because this was developed from scratch with using lots of new ideas, and also developing some new technologies to enable us to, to, to do this. They would be fitted with a continuous glucose monitor. So this would continuously measure their glucose for the two weeks of their home. They would have also a Physical Activity Monitor that also measured sleep duration and quality. And they would also be set up to our dietary assessment app, which was designed by Zoe, the tech company behind the PREDICT studies. And over the two-week period, they would be asked each morning, after an overnight fast to consume one of our standardized muffins. And these varied from day-to-day nutrient composition, so in the amount of protein, fat, carbohydrates, and fiber. And they also have these in duplicate.

And this was really important because what was very important for us to see is how much of the variability in people's responses is due to day-to-day variability. So how much is what we call intra within the person variability, and how

much is due to between person inter-individual variability. For precision nutrition to be effective, there has to be less within person variability than between person. Otherwise, it's not possible.

So these muffins were given in duplicate so they would have over in two separate occasions, a muffin might be high fiber, than they might have on two occasions a muffin that would be high protein etc. And obviously, a randomized order. And then, the rest of the day after four hours after consuming the muffin, then they were free to really do consume and practice their normal dietary lifestyle habits. And what they did was they would also record everything they ate and everything they drank during this time period. And the dietary assessment app that we used integrated various ways of monitoring diet, so it integrated weight records, barcoding, and also pictures as well.

And this was really important because as many nutritionists will know, at the heart of nutritional research is actually trying to capture dietary intake effectively. If we can't monitor what someone's having, how can we predict its response? And we built this live dashboard. And we had a whole team of nutritionists who in real time would actually monitor what participants were putting into the app, which was fantastic. So if Danny, for example, you said that you had a burger and some chips, and you gave, you know, a set portion size, but actually, your picture showed that your portion size was actually 10 times more, what chips you had put down, which would be cool down to importing, then the nutritionist in real time keeping your message and say, “Can you just check that?” And you could go back and say, “Well, okay, sorry, I have actually had two plates of chips, and not just one.”

And so it meant that we were able to capture people's diet at a resolution that just hasn't been done before at this scale, which is really,

really important, and which is, I think, really important to bear in mind when we think about the latest studies that that I discussed that we're capturing such high resolution data. And so from this, we've captured dietary assessment data. We've captured there for metagenomic data from the stool samples, metagenomic data, and, you know, how we eat data so time of day, activity, sleep, etc.

And just to give you an idea of the scale of the data that we've collected from PREDICT-1 alone, we had 32,000 muffins consumed from these 1,100 participants. We had 132,000 meal logs, meals logged. We had over 2 million continuous glucose readings collected. And we had over 28,000 triglyceride readings from the dried blood spots that we collected. And all of these went on to produce thousands and thousands of more data points. So we have millions of data points. And this is where the AI then became really valuable. Because as a nutritional scientist, I don't too many of my colleagues would not have the expertise to then actually, we've collected all this wonderful data, what Earth do we do with it? And I struggle with my end of 20 studies, never mind these thousands of data points. So this is what's fabulous about this kind of union between traditional academic researchers like myself, and a tech company like Zoe that they can take this fabulous data and do something, you know, do the data justice.

DANNY LENNON: Just before we get to the results, I think there's two things I just wanted to touch back on and emphasize. I think one aspect that is really cool that you mentioned is around the dietary assessment. And I think many times on this podcast, we've discussed the issue of underreporting, and even people who are practitioners from a pragmatic standpoint, know the issues that trying to get people to report food intake accurately. So I think that adds a very interesting aspect to this. One kind of sidebar maybe to take before we get to the results. Just because I know I think a lot of

people in our audience would find interesting, from a pragmatic perspective of doing nutritional science research relates to something already mentioned, but I think it's worth emphasizing around the muffins that you've often used within some of your research, and the reason why that is selected or why that is such a useful way of having a food source that you can easily modify and, and change the nutrient composition of that works so well, as opposed to doing some other form of that. Can you maybe just reiterate that for people and give some more of the details about that?

SARAH BERRY: Okay. So the reason we use muffins is because we want to deliver nutrients in the most simple possible way. So the food matrix is so, so complicated. We know that we don't consume single nutrients. We don't consume single foods. We consume dietary patterns. And we know that looking at single nutrients within a complex food matrix introduces so much variability. What we wanted to do as a starting point for PREDICT was to look at, look at the impact of different nutrients, as well as foods, which is using the free living data that we collected from PREDICT.

And so we wanted to look at this in the most simple possible way. And using muffins is a really simple way to deliver a variable amount of a simple nutrients without the complexity of the food matrix. And the reason we don't want the complexity of the food matrix is because we know it has a really powerful effect on how we respond to food. And if I can use nuts as an example, just because I've done quite a lot of research on nuts, so that that is a food I find particularly interesting in terms of the food matrix. If I was to consume a whole nut or a portion of a whole nut, I would actually excrete 40% of the fat. Okay, because the cell walls that are within nuts are so rigid, they retain the fat within them, and they're quite resistant to the enzymes in our intestine and they come out the other end.

Now if I was to mash that nut up really fine, like into a fine powder or butter, I would actually absorb nearly all of the nuts. Now on the back of pack labeling, it would look identical, they would both say 50 grams or the 100 grams is fat. You know, X amount is carbohydrate. X amount is protein. But how my body handles it is totally different. So the whole nut I will absorb very little of the fat. I will also have a really tiny lipemic response. And we've actually studied this. I had, I had a study published about 10 years ago where we compared that lipemic response to whole nuts versus finely ground nuts. And you had, I think it was about 55% difference in the level of lipemia between the two. But they were identical ingredients. They were identical nutrients, but they were not identical in the matrix. So the form in which they were fed.

So what was really important when we were designing the meals for PREDICT is, we don't want this complexity from the food matrix. We don't want to start introducing complexity for cell wall structure or the complexity of the dairy protein matrix. We want something really simple, so that we have the best starting point from which we can start to unravel these differences. And so that's why we decided muffins are the best option because we can just add in very refined simple fat, simple carbohydrates. And we can alter the amount of these to alter the relative nutrient composition without any of the other complexities.

DANNY LENNON: Brilliant. Thanks for clarifying that thing. It's really valuable for people to see some of the insights into actually doing good nutritional science. So with that, for the results from PREDICT, what from an overview level are some of the most important things to emerge from that, can you maybe run us through a few of the results that came from it?

SARAH BERRY: So I think the key points that we found, and if you want to, we can delve into more that if you want to pick up on any of these in detail, is that

there are significant variability between individuals. So there is a huge variability in how people's triglycerides, glucose, insulin responded. And what was really interesting here was that their postprandial responses, so their six hour triglycerides, or their, their 30 minute glucose is far more variable between individuals than the fasting level. So if we think of it in terms of coefficient of variation, at baseline, for example, for triglycerides, the variability between individuals, from a CV perspective is about 50%. But at six hours it doubled, is about 100%. So this was kind of a really important finding in that while there's massive variability, but the variability is even higher postprandially, suggesting that actually, if we can look postprandially gives us better sensitivity from which we can, you know, separate out people that have poor metabolic response versus those that have good metabolic response.

A second key finding was that the within subject, the intra-individual variability is far less than inter-individual variability, which is what I mentioned earlier that for precision nutrition to be effective, we need to ensure that in our measure of interest, or in our responses to food, that actually the between person [00:38:38 independent] variability is greater than the within person variability. And we found that.

And we then started to explore, okay, we've seen that huge variability, we've seen that there's more variability between them. Within people, what's causing this variability? And this is really the core of our findings, where we were able to actually unravel what are the key determinants. And we were able to do this because of the breadth of data, but also the depth of data and the scale of data we had. So we started by looking at the impact of genetics. We've also looked at the impact of the microbiome. We've looked at the impact of how we eat. So this is something that particularly interests me. So how does X size, time of day,

sleep, stress, how does all of that impact it? And then we've looked at person characteristics, so age, sex, BMI.

Now, many of these factors have been looked at in other studies where they've looked at single inputs or single outcomes. But we've looked at these relative to each other. So how important are the genes, you know, or, or is our DNA compared to these other factors. And what we've also looked at is once we see how important they are and how they're modulating our response, how does modulating that response impact downstream health factors. And we've also explored that for a number of variables such as hunger, energy, intake, inflammation, lipoprotein remodeling, as well as many more.

DANNY LENNON: So the fact that we see these differences between individuals, and we know there's a variety of different factors that can potentially influence that from genetics, microbiome lifestyle, other factors that you mentioned, maybe not be that surprising to some people. But I think one of the big things is trying to kind of quantify what is the magnitude of the effect of each one? Because as you say, there's been other work before that's alluded to, oh, this thing has an influence, but trying to work out well, what is the magnitude of effect? Are we at a point where we kind of know how much of this is contributed by genetics? How much are things outside of genetics and so on? Can you maybe tease apart that for us?

SARAH BERRY: Yeah. i think you've hit the nail on the head that, like I said, that there has been work on this before, but it's looking at the single variables. And it is really important, we understand, in my opinion, what the relative impact is. And this is important for, I think, practicing nutritionists, so that they can actually give advice based on actually what's going to have more impact, because you don't want to spend all your time making some sort of modification to your diet or lifestyle when it

actually only has a small impact. And so we can walk through each of the kind of key variables that we looked at.

So the first one to mention, I think, is genetics. So as I said earlier, we have this wonderful resource of the TwinsUK, TwinsUK cohort of identical and non-identical twins. And so what we were able to do is we were able to look at how much of people's responses was actually due to genetics. And we could do something called Ace heritability modeling. So as well as looking at individual snips, we could look overall, how much is due to genetics, how much is due to shared upbringing, and how much is due to none of these factors, so it's totally independent. And this is because we had identical, non-identical and also unrelated individuals in our study. And I think it was actually really surprising that actually very little of the effect, certainly for triglycerides was due to our genes and less than 2% of our postprandial lipemic response was due to genes. When we looked at glucose, we found that less than 50% was also due to our genes.

And I find this really fascinating as a 70s child that grew up in that time that well, you know, genes have just DNA has just been discovered. And, you know, or rather the, you know, the mapping of this has been discovered, and it's all about genes. So I was very much kind of 80s child that was told, "Well, it's all in your genes. There's nothing you can do about it." This shows it's not all in your genes that actually how we respond to food that there's a small contribution, but actually we have, as individuals control over how we respond to what we eat. I think that's a really powerful. And I think, you know, it's unfortunate that there's a lot of products on the market that, you know, these DNA testing kits that will, will tell you how and what you should eat when? Yes, they might tell you a fraction of how you might respond. But I think, personally, they're actually a little bit of a waste of money, because

they're only telling you a very small picture based on our research. Yeah.

DANNY LENNON: I think that's a really valuable point, because I think it oftentimes does a major disservice to the concept of personalized nutrition, which is very much legitimate. But sometimes that term gets co-opted by these groups who have said, oh, here's a consumer DNA test. And as you say, we'll, we'll give you a full diet of exactly match to your DNA. And like, this is the way you should eat. And neither the science is there, or as you say, there's other factors that are more important. And so I think it's important for people listening to realize, to not to immediately dismiss looking at genetics or personalized nutrition on the basis of seeing some of these fringe areas that co-opt the term, and stick to like what we actually are seeing which very much has some very interesting work being done.

SARAH BERRY: Definitely. I think that personalized nutrition, where we're capturing all the different determinants. So microbiome DNA, person characteristics, I think, is a very valuable and is the way forward for nutritional research. But and I think we must be very mindful not to be put off by, you know, this sense that personalized nutrition is about DNA nutrition. It's not, it's way, way more than that, and we now are at this point in time where we can capture way, way more than that. So we really do have the power now to go beyond that.

DANNY LENNON: One other thing I was going to mention before I let you back to your point was you said that was differences at based on our fasting differences, that variation was much smaller than when we look in the postprandial period. And that again highlights your point earlier that you mentioned of the importance of considering the postprandial response to meals as opposed to just fasting blood measures, kind of reminded me of, I had a conversation with Nicola Guess around diabetes and pre-diabetes and nutrition. And she mentions this capacity

where you could have two people with very similar fasting blood glucose. You look at then a two hour oral glucose tolerance tests and their postprandial responses much, much different, which would have differences in terms of the intervention for the practitioner of how we may classify one of those people, and how, how urgent intervention may be needed. And so again, it speaks to this need to not just consider maybe some of these fasting markers, and some point you made a couple of times, so just wanted to re-emphasize that for people that thought it was particularly harm.

SARAH BERRY: I think it's a really valuable point, because we do see, you know, with all of our outcomes very closely tied together, fasting values, but where we get the discrimination is in this postprandial phase. So how could we have told that person A, who has this massively high postprandial response, but the same fasting responses, Person B, who might have a really low postprandial response? Exactly, as you described, Nicola had said, it's not until we look in that postprandial phase that we can really differentiate people's metabolic control and their subsequent health outcomes ultimately.

Okay, moving on from, from genetics, we saw that genetics had a role to play, but a relatively small role to play. We also saw the role that the microbiome played in our postprandial responses. And interestingly, we found that the microbiome had a larger impact on our postprandial triglycerides or a lipemic response. And it did actually our glycemic response. And this is a really novel finding. Nobody's looked at this before. So we have known from a very large study that was undertaken by [00:47:10 ZV's group], it is well that the microbiome had a significant impact on the glycemic response. But we saw that it was even higher for the lipemic response, which I think is really exciting novel findings from this work.

And what we were able to do, as I mentioned earlier, is look at the relative contribution. So how much is due to the genetics and microphone, how much is due to sex, age, BMI, how much is due to your long-term diet intake, and how much is due to how we eat. And we found that the ranking of these determinants was different depending on the outcome. So, for example, genetics was important for glucose, but it just was not relevant for triglycerides. Yet, the microbiome is highly relevant for triglycerides, and although relevant, slightly less relevant for glucose.

So what this enables us to do is later down the line, we could look at people that have poor glucose control, and we could look specifically at the determinants of what controls that for glucose control in that individual. And it -- they will be different to how we would treat and advise someone that has poor lipemic control, because there's different determinants. And I think that's really important that finding that we were able to reach. And ultimately, when we put all this together, when we used our machine learning expertise, we could also build a model to predict someone's individual response to a given meal using these various input factors. And what we found is we could predict with about nearly 80% accuracy, so about 77% accuracy, someone's response versus their predicted response, which is really exciting, I think, you know, there's a high level of accuracy.

DANNY LENNON: Off the back of some of those findings and some of the conclusions that you may be able to come to, obviously, that has led on to further sub-studies and then PREDICT-2 and PREDICT-3, for some of those other research questions that were being attempted to be worked out. What were they, and how kind of how does that lead on from the initial PREDICT trial to what questions needed to be answered next, I suppose?

SARAH BERRY: So there's loads of questions to answer next, and we have a lot of data to be able to answer them. It's a case of, you know, addressing one by one, which then leads us on to a new questionnaire, finding a new answer, and it's rather never ending, but really exciting that we have this amazing data resource. We've been looking at factors such as time of day, and we're seeing some really exciting findings about how time of day is important, which we already knew, but also how much variability there is between individuals. And we see that some People are really susceptible to time of day and some people aren't. We've been looking at how the timing, the duration of exercise impacts different responses and how again, it's different between some individuals and other individuals. We've also been looking about the shape of the curve. And I mentioned this earlier, so the shape of the glucose curve and how that impacts things such as hunger. And so we can predict how hungry someone might feel after a meal, how many calories they might consume over the next 24 hours based on the dip in glucose that they have two hours after having a meal rather than their overall glycemic response.

There's a lot more factors that we're looking at. We're looking at things like meal sequencing, and sleep in particular as well. And we've designed the follow-on studies such as PREDICT-2 and PREDICT-4, with the findings of the first study in mind to really start to delve into these deeper. So we've seen how powerful time of day and meal sequences from PREDICT-1. So PREDICT-2 was designed to delve into this even more. And we've had within PREDICT-1 some sub-studies like PREDICT - Carbs that was specifically designed to delve even more into meal sequence as well. And ultimately PREDICT-3 is a study that's capturing everything that we've learned from PREDICT-1 and from PREDICT-2. It's an exclusively at home study. And it's translating many of these findings into kind of more of a real life context. And so that we can really

produce actionable advice for people after this. And that's what's really exciting with the joining all of these dots together, that we can actually from this tell people based on all of these determinants, this is what we recommend for you as an individual.

DANNY LENNON: We've obviously got a lot of this really fascinating and interesting findings, lots of these interesting research questions that have been generated, lots of interesting hypotheses, and kind of a clear path forward from an academic sense of what you're trying to investigate and more stuff to work out on the side of for practitioners and implementation of this work down the line in dietetic practice or with medical professionals. What does that potentially look like going forward? And what do you think needs to happen in between to kind of bridge that gap from the stuff we're starting to see now versus getting to a point where it's actually actionable, let's say in a dietetics practice?

SARAH BERRY: So we do have further to go. The work that we're doing is very specialized at the moment, but the, the fact that we can implement this in an exclusively at home remote setting shows that it is something that is attainable, or rather achievable. So whether it's attainable full is another matter. And I think the important thing that we need to think about is that if we have collect -- once we have collected all this data, once we do know what determines a person's response to food, does it actually result in meaningful change? And I think that's something really important before we almost try and join the dots. Because if it doesn't result in meaningful change, well, what's the point of everything that we're doing?

And there's a EU program called “Food for me” that looked specifically at this. So they randomized participants to four different groups where they had three groups that we're having a personalized dietary advice, whether it was diet only, diet phenotyping, diet genetic-

based advice, and then people that had no advice. And what they found was that those that were having personalized advice, and this was personalized from the dietitian, actually performed a lot better in improving their diet, and people have no advice.

Now, they didn't have big differences between whether it was diet only advice versus diet and genetic and phenotype advice. But it still demonstrates the efficacy of having that personalized advice. So we know from that large, large program work that it does work. We're collecting the data to make it work. And now what we need to do is try and ensure that this is something that is attainable for everyone.

DANNY LENNON: Can you maybe let people know where they can find more information about you on the Internet, more information on the trial, etc. Any places that you'd like to divert their attention, social media, ResearchGate, etc. Where are some places they should check out?

SARAH BERRY: There's a lot of information on the PREDICT program of research on the Join Zoe website, which is joinzoe.com. I would point you in the direction of our science paper. The science paper really covers everything I said today, but a whole lot more on the genetics, and particularly on the microbiome, which I've only just touched on. The microbiome is a huge part of our research. And we've got some really exciting findings on microbial signatures, health and diet. That's all summarized in the white paper. For myself and my research, I'm on the King's College London website. And you can also follow me on Twitter on Saraheeberry is my handle.

DANNY LENNON: Perfect. And for everyone listening, I will link up to everything that Dr. Berry has just mentioned there in the show notes of this episode, I recommend you go and check that out. So with that, we come to the final question. I always end the podcast on. If you could advise

people to do one thing each day that might have a positive impact on any area of their life, what might that one thing be?

SARAH BERRY: Okay. So, in terms of diet, my, my one thing for diet would be enjoy what you eat. If food is there to bring you pleasure, it's there to be enjoyed. It's not there some to fear or to be overly controlled. And the second thing would be physical activity. Do some sort of physical activity every single day.

DANNY LENNON: A wonderful way to finish. And let me, let me say, Dr. Berry, thank you so much for not only your time today, but for the great conversation and for your work that you've done up to this point. It's definitely been informative for me. So I very much appreciate it.

SARAH BERRY: Pleasure. Thank you, Danny. It's been fun talking to you. I'll work with you. Thank you.

[00:56:29]