DANNY LENNON: Dr. Kevin Hall, welcome back to the podcast.

KEVIN HALL: My pleasure. Thanks for inviting me back.

DANNY LENNON: Kevin, maybe to start this off, if we think about what the aim of the study was, and more specifically, what was this study set up to address, and just as importantly, what was it set up not to assess.

KEVIN HALL: Great way to start that, because I think a lot of people take the results from our studies very much out of context. So this was, first and foremost, not a weight loss study. So a lot of people see words like plant based low fat diet versus animal based ketogenic diet, they immediately assume, oh this must be some sort of weight loss study or something like that. That's not what this was about. We typically actually don't do weight loss studies. My lab is more interested in trying to understand the basic physiology of how the body adapts to different diets, both in terms of metabolism as well as more recently we focused our attention on what regulates how much people eat over a period of many, many days at a time. And so, this study was designed to address the latter question of what is it about our food environment that has been driving the obesity pandemic for the past several decades. And

there's lots of different theories about that, and this study was really designed to kind of test how very controlled manipulations of the food environment in a very artificial setting that is the metabolic ward at the NIH Clinical Center, how do those manipulations influence people's ad libitum energy intake. In other words, how do they influence how many calories people choose to eat when they're not really trying to change their body weight or trying to change their lifestyle at all, they're just basically given very simple instructions to just eat as much or as little of this food as you'd like.

DANNY LENNON: I think that's a crucial part that you mentioned about we're looking at this regulation of energy intake, and you also mentioned that there are various theories about how we can manipulate diet to potentially impact that regulation. So when we look at the specific diets chosen for this study, essentially, why this study, why these diets, why were those selected to answer this particular question?

KEVIN HALL: Yeah, so there's a lot of work that goes into designing these studies in these particular diets, to address this question. But what I'll do is I'll kind of discuss the two particular hypotheses that we were trying to address with this study in terms of why it is that some people think changes in our food environment have led us to overeat and thereby gain body weight, at least, that's my hypothesis for how this goes. One of them is, well, they're actually both relatively old ideas. One of them was most popular, I would say, probably in the late 1980s, early 1990s, something called the passive overconsumption model of obesity. And in that model, the idea is that if you are presented with a food environment that has a very high calorie density, typically a higher fat diet, because fat as your listeners probably know has more than double the calories per gram than carbohydrate and protein. And when you also consider the fact that most foods that have a lot of carbohydrates and protein are also bound up with a bunch of water, which

dilutes their calorie density even more, higher fat diets tend to have many more calories per gram of food. And so the idea was that if you consume a diet that is very high in energy density, and typically, although not always, that means that it's high in fat, you will, for every bite of food that you eat, you will be eating more calories. And if you, therefore, kind of passively eat your food and eat the same number of grams as you would normally eat, you will thereby overconsume calories and gain body fat as a result of that.

So that's one idea of why people might gain weight and gain fat on a high fat, high energy dense diet. Another idea that's been more recently popular is the carbohydrate insulin model of obesity, which postulates that no, no, it's not really about the energy density, it's not really about the fat in the diet, it's really about whether the diet leads to big increases in insulin after meals, so called postprandial insulin. And the thing that that model postulates is primarily responsible for elevated postprandial insulin is very high glycemic, carbohydrates, often processed carbohydrates in the diet, but not necessarily processed. But high glycemic carbohydrates will tend to increase your postprandial insulin and that will thereby according to the carbohydrate insulin model, divert calories into fat stores because of insulin's effects on adipocytes, and that will be sensed by the rest of the body as a calorie deficit. So any non-adipose tissue in the body, like muscle or liver or the brain, will sense a deficit in calories available because they have been sequestered in fat cells because of the high postprandial insulin, and therefore, that will lead to a decrease in the number of calories that you're burning in terms of your energy expenditure and will also lead to increased hunger and thereby eating more calories as a result.

So we have these two very different models of obesity. One which postulates the main player is the carbohydrates in the diet, the high

glycemic carbohydrates, causing large postprandial excursions and insulin, which will then lead you to become hungry and overeat; and the other, it's the fat in the diet and the energy density, which leads you to passively overeat. And so, the idea for this study was to take two diets that are very different in terms of both their energy density and their fat content, as well as their ability to secrete insulin after meals and basically put them head to head and see whether people spontaneously consume more calories on one of these diets than the other and gain weight and gain body fat, and put these two models to the test in some sense. And so, the way that we designed those two diets was to try to look at two diets that are actually commonly recommended for people with obesity, to treat their obesity, and try to design diets that kind of mimic those popular diets at the current time, and one is ketogenic diet that is typically high in fat and very low in carbohydrates and often includes a lot of animal based products to make up the majority of the calories; and the other is the so called whole food plant based diet which is devoid of animal products, so it's a vegan diet, but it's very low in fat and very high in these high glycemic carbohydrates. But both proponents of these diets might differ a lot in many respects in why they think their diets work. They both actually are recommending that they be relatively low in ultra-processed foods. So we designed both of these diets to be low in ultra-processed foods. And they also recommend a lot of non-starchy vegetable intake, and so we actually match the two diets for the amount of non-starchy vegetables. So we're really trying to get at kind of exemplary versions of both the ketogenic diet that is recommended, the so-called well-formulated ketogenic diet, and these plant based low fat diets that are being used.

DANNY LENNON: So if we look at the actual setup of the study, you already mentioned that this was a metabolic ward study, can you maybe just give some more of the overview of the study design,

and then just to clarify for people, the degree of control that's offered by something like a metabolic ward?

KEVIN HALL: Yeah. So since we're now focusing our attention on food intake regulation and how the body decides how many calories to eat, we actually have to keep people in an inpatient environment in a so called metabolic work, because we unfortunately don't have objective and quantitative ways of measuring people's calorie intake when they're kind of going about their daily life. So it's one of those unfortunate realities that we have to deal with, which is if you really want to measure what people eat, really, the best way to do that is to kind of bring them in, don't give them access to any outside food, basically monitor every morsel of food that they eat. And so, what we did in this study was bring 20 people in to the NIH Clinical Center, they stay on this metabolic ward, which is basically like a hospital ward, they each get their own room; we don't study all 20 at once, which is another problem. But what we do is basically they come in, and in this particular study, they didn't know what the purpose of the experiment was other than that we were interested in how two different diets affected their body. And for 28 continuous days, 24 hours a day, seven days a week, we stayed with them, or they stayed with us, sorry, we didn't stay with them, stayed with us, and basically, they were given three meals per day and snacks to eat if they wanted, and simple instructions, just eat as much or as little of this food as you would like. They were blinded to their measurements of weight, they were blinded to their measurements of glucose, ketones, all of these other measurements that we were making, so they couldn't necessarily use any sort of feedback along the way to try to change their behavior. But basically, for the first two weeks, we randomized them to either the plant based low fat diet versus the animal based ketogenic diet. And for the second two weeks, they switched to the opposite diet.

DANNY LENNON: So within that we have obviously this crossover design that you just outlined. They're in a metabolic ward, everything is being measured tightly. With relation to the administration of the diet, here we have a situation where we're looking at ad libitum intake so people can consume as much or as little as they wish, but we also are trying to standardize probably what's available to those people. Can you just clarify for people if they're unsure of how you go about administering diets that are as comparable as possible, in relation to, say, calories, protein, etc., the amount of starchy veg, like you mentioned previously, but also allow it to be ad libitum?

KEVIN HALL: Very few of these studies actually get done, so there's only a handful of these kinds of studies that have been done in the past, and never ones that are looking at these two kinds of diets. But the basic idea was, look, we've clearly got to provide them with more calories than their bodies need, because if they want to, you know, if we want to test whether or not people overeat on one of these diets and thereby gain body fat, we would likely have to provide them with more calories than their bodies are burning kind of at baseline. And so, what we did was we measured everybody's resting energy expenditure, and we've standardized a, in our studies from the past, a routine for them to do, including 60 minutes of cycle ergometry at fixed wattage every day, so that we know, basically, how many calories they're going to burn. And so what we did was we doubled that number for every individual, and we said, we're going to design two menus that have the same number of calories, that have the same amount of protein, that have the same amount of non-starchy vegetables. But in one case, we're going to have a very low carbohydrate content, 10% carbohydrates, total carbs, not net carbs with total carbs, and 75% fat which would be – and most of the, about 80% of the calories are coming from animal based products, meat, fish, eggs, dairy, that sort of thing.

And so that is our animal based low carb diet, which kind of is also being tailored to – it was, again, minimally processed foods, kind of tailored to what a lot of people who recommend a well-formulated ketogenic diet would recommend. But it also, because of the high fat content, tends to be very high in energy density. So roughly two calories per gram for the non-beverage energy density. On the other side, we basically said, we're also going to present you with the same amount of protein, the same amount of non-starchy vegetables, but this time, we're going to add plant based products to make up all of the calories, but there'll be starchy sort of plant based products and legumes, so lots of sweet potatoes, quinoa, grains, that sort of thing to make up the bulk of the calories, and thereby generate a high glycemic index or high glycemic load diet that will likely cause much higher insulin secretion, but because it contains relatively little fat, will have a much lower energy density. So that's how these diets were designed.

DANNY LENNON: So just as a recap for people, we have these two diets, the animal based ketogenic diet was around 75% fat, 10% carbohydrate, and an energy density of around two calories per gram; and then the low-fat plant based diet was 10% fat, 75% carbohydrate, and about one calorie per gram, so about half the energy density;; and they were matched for protein in terms of what was made available to participants. So one final thing before we get to some of the results, Kevin, in terms of the primary outcomes that were listed, we obviously have mean energy intake over the two-week period between the two diets, but then you also had, as a primary outcome, energy intake, specifically, during the second week of both diets. Can you maybe just touch on why that was selected, and the relevance of that?

KEVIN HALL: Yeah, sure. So a couple of reasons for that. But I think the primary reason is that one of the things that we've known from our previous

studies is that it takes about a few days of a ketogenic diet to kind of get above the sort of threshold of defining state of nutritional ketosis, which I think most people say is circulating beta hydroxybutyrate level of above 0.5 millimolar. And so, what we wanted to do was give these folks some time to adapt to the ketogenic diet, and we actually included several different measures, so that we could assess whether or not people had adapted to the ketogenic diet in that second week. And so, the idea was, look, let's give that diet a chance, we've had previous criticisms of our other studies saying that you just – you haven't given people long enough to adapt to a ketogenic diet, ketones rise for many, many weeks at a time and starvation, and we can discuss that, it's actually not the case in ketogenic diets. But yeah, so we wanted to basically say, look, let's wait for ketones to rise to a certain amount because one of the mechanisms that people suggest by which ketogenic diets reduce appetite is because of the circulating ketones per se. So we basically pre specified that we would have two primary outcomes as we said, one, which would be the entire two-week duration on both of these diets, and the second one is only looking at the final week of both diets to allow both the ketones to increase, but we also wanted to also have this issue if we didn't have a washout period between the two phases, and we wanted to allow for any carryover effects that might have taken place from transitioning from one diet to the other to have at least petered out by the end of that first week on the second diet.

DANNY LENNON: If we turn to some of the results, first off, we mentioned how the diets that were made available, were kind of broken down, how did the actual consumed diets compared to that of the food that was made available in terms of some of those nutrient breakdowns we've already referenced?

KEVIN HALL: Yeah, they were very close to what was provided, with the one exception being that

even though we provided the same amount of protein in both of the diet groups, during the animal based ketogenic diet, people consume slightly more protein, statistically significantly more, both in terms of an absolute amount as well as a percentage of total calories. So they were eating a slightly higher protein diet than they were during the low fat, plant-based diet.

DANNY LENNON: So let's talk about those two primary outcomes that we've just mentioned, the average energy intake over those two weeks, and then the second week energy intake specifically, what were the findings from your study?

KEVIN HALL: Yeah, so maybe before we do that, let's review the predictions of both of those models. So the prediction of the passive overconsumption model is that because the animal based low-carb ketogenic diet is very high in fat and very high in energy density, people should therefore overconsume calories, eat more calories than the alternative lower energy dense lower fat diet, and gain body fat and gain body weight. The alternative carbohydrate insulin model suggests that if the lower fat diet has high amount of high glycemic carbohydrates, then that should lead to much greater insulin secretion after meals, and that should drive the hunger because of the sequestration of calories inside fat tissue, and people should accumulate body fat and eat more calories as a result. So those are the two predictions, and what we found was that neither prediction ended up being true. In one case, the diametrically opposite prediction turned out to be true. In the other case, we just didn't see any body fat gain. So the overall result was that despite the predictions of the carbohydrate insulin model, with respect to ad libitum energy intake, we found that the people on the low fat diet, despite having much, much higher secretion of insulin after meals and throughout the day, ended up eating almost 700 calories per day less than the animal based ketogenic diet. And that's over the two-week period and a little more than 500 calories per day less, just

looking at the second week. So that's the top line sort of those two primary outcomes.

DANNY LENNON: There's an important bit of context there of how to interpret those findings, and particularly in relation to those two hypotheses that we mentioned earlier. You mentioned that there is that kind of difference observed within the second week in terms of the amount of difference there. Does that give us any indication or is there any credence to some of the claims related to some of those that would be in the low carbohydrate community?

KEVIN HALL: It's certainly possible. So it's one way to interpret this, and I'll just describe this a little bit more. One of the things that we found was that when the people were on the low fat diet, the amount of calories that they ate, on average, across these folks, did not change significantly over week one to week two. So they basically ate more or less, on an individual basis, people are eating more and less each day, but when you average it out over the 20 individuals, the mean on each day was basically the same throughout weeks one and weeks two. But in contrast, during the ketogenic diet, people were eating quite a bit more calories during the first week than the second week. So, in fact, when you compare those two weeks, it was about 300 calories per day difference. So there was a drop from the first week to the second week of about 300 calories per day and, of course, that coincides with the rise in ketones that we observed in the blood which, basically, were rising during the first week, quickly surpassed the 0.5 millimolar, beta hydroxybutyrate threshold, and then were relatively stable during the second week. And so, that's an association between the increased ketones and the drop in calories between weeks one and weeks two, but we can speculate that maybe that's the appetite suppressing effect of ketones kicking in, although we can't demonstrate causality in that particular regard.

DANNY LENNON: Sure. In terms of some of the other markers that were mentioned, given the type of hypotheses we've mentioned and how they're suggested to influence hunger or appetite, what were some of the findings related to some of those measures?

KEVIN HALL: So the idea there was maybe people were just, they had very different reports of hunger and fullness and an eating capacity and things like that, but actually, what we found was that there was no reported differences in these repeatedly visual analog scale measurements before and after meals over the course of many hours. People did not report any significant differences in hunger or fullness or eating capacity or desire to eat those types of measures over the course of the study. They also didn't report, one might say, okay, well, maybe they just liked one of the diets more than the other. Of course, the low fat plant based diet was just really yucky, and therefore, people didn't eat as much of it because they liked the ketogenic diet so much more. That didn't turn out to be evident in the data either. People reported the pleasantness of the meals equally on the two diets. There was no significant difference between those. And we actually, before admitting these subjects, we made sure that they were sufficiently familiar with most of the foods that would be delivered so that they didn't have some sort of neophobia of, I've never seen quinoa before in my life or I've never eaten that kind of fish before or something like that. And therefore, when we asked them how familiar the meals were, they basically rated those equally as well. So it didn't seem like we were just observing some obvious effect on pleasantness of the meals or familiarity of the meals driving this effect. It wasn't obvious that they were rating the meals equally in terms of their response to hunger. But of course, they were eating many, many more calories on the ketogenic diet meal. So on a per calorie basis, of course, it seemed like the lower fat plant based diet was leading to a kind

of better regulation of appetite, if that's the way you want to interpret the data.

DANNY LENNON: Given those differences in the amount of calories that were consumed, we can infer that subjects basically ate less on the low fat diet, but as you've outlined, really, this study is set up to evaluate those competing theories that we've referenced already, and there's also no claim here made about why subjects ate less. So at least, from my reading of the paper, it's not like you're saying, this is the specific mechanisms by which we know subjects ate less on this low fat diet, because essentially, that wasn't the question of this particular study. Is that accurate?

KEVIN HALL: Yeah, I think that that's accurate. I think that we should also maybe explain a little bit more about what ended up happening in this study, because you said that they ate less. They ate less calories on the low fat diet, but they actually ate more grams of food. So it just turned out that because they were so much lower in energy density, they ate more grams of food, but they ended up eating less calories on the low fat plant based diet. So that might partially explain why they felt equal degrees of being full despite eating fewer calories, they were eating more grams of food. They're also taking a little bit longer to eat their meals, and their eating speed in terms of grams per minute was actually faster or slower, but the calories per minute that they're eating their food was lower than the ketogenic group. So there were differences in the rate at which people were eating the meals as well. And some folks have hypothesized that it's really the eating rate and the kind of orosensory properties of the foods and how quickly you consume them, that is a key factor. But you're right, we cannot determine what the mechanism was, or we didn't determine what the mechanism was in these two diets that led to such stark differences. I mean, the other thing to kind of wrap your head around is that these are not small differences in energy intake. We're

talking many, many hundreds of calories per day. Who knows how long that difference would last? If it would persist for many, many, many weeks and we run the study much longer, we don't know the answer to that question. But these are not small effects, and there's a lot of hypotheses about why we saw the effects that we saw, and I think it's kind of useful to kind of put the study in context with previous studies that we've done as well as many other people have done to try to come up with some hypotheses about what the mechanisms might be.

DANNY LENNON: For sure. I think that energy density finding is really important, and like you mentioned, that total mass of food, such a wide discrepancy, I think the plant based diet was over two kilograms where it was like 1.5 or in and around that for the ketogenic diet, so significant difference in the amount of food in terms of actual massive food. And on the podcast before we've had Barbara Rolls talk about some of her work in relation to food volume, energy density, and so on, so there's obviously a basis for that for sure. So it kind of sets the stage nicely, I think, for further questions there. In terms of some of the interpretation of the study findings, we've referenced some maybe misinterpretations, but we can get to maybe more of those in a moment from you and your colleagues, what do you think are the kind of couple of big things that you took away, and you'd ideally like people to take away from this specific study, and then as a kind of second part to that, where do you maybe see some misinterpretation, or maybe people picking up the wrong idea from this particular study?

KEVIN HALL: Right. Yeah, so, I mean, I think that a couple of the take-home messages here were the predictions of the carbohydrate insulin model were being tested by the low fat plant based diet. So that diet is the one that's supposed to lead to much higher levels of insulin after meals, and we clearly observed that and is

therefore, according to the carbohydrate insulin model, supposed to lead to excess hunger, increased calorie intake and body fat gain. And those predictions just did not turn out to be true, so it's not that the carbohydrate insulin model was making predictions necessarily about the low carb ketogenic diet; it was making predictions about the low fat plant based diet. And I found it interesting that a lot of the pushback that we've received on this has been saying, oh well, the ketogenic group hasn't been fat adapted yet, and we can discuss various measures that we had in this study to kind of demonstrate a substantial degree of fat adaptation. But they missed the point that that wasn't really the diet that was testing a hypothesis. It was the other diet that was testing the hypothesis, and I thought that all these insulin surges after meals were supposed to make you ravenously hungry, and that clearly didn't happen. So I think the point is this is another demonstration, I think that that idea of carbohydrates driving postprandial insulin which drives hunger and therefore other aspects of the diet are of minimal importance in terms of generating adiposity, it clearly didn't happen in this case. Despite very large swings in insulin and glucose after meals by design, these people were not ravenously hungry, they ended up cutting calories and losing a substantial amount of body fat.

On the other side, if you were a proponent of the passive overconsumption model and kind of a skewing high fat diets, well, this was a very high fat diet, the animal based ketogenic diet. They did not gain any body fat. They lost weight, most of that was fat free mass, but they did not overeat and gained body fat. So if that was the diet that was testing the prediction of the passive overconsumption model, and that prediction also did not turn out to be true. So I think that that's an important takeaway is that we sort of ended up with what I think is an interesting study, testing two different hypotheses for obesity that both of which I think contain hints of truth to them, but both

of them were insufficient to explain our data. It doesn't mean that energy density isn't important. It doesn't mean that insulin and carbs aren't important. It just means that what's regulating people's appetite and regulating calorie intake when you do these kinds of studies, by manipulating people's food environment, and not allowing them access to other kinds of foods, is more complex than can be explained either by energy density alone or insulin secretion after meal is driven by carbohydrates.

DANNY LENNON: With relation to some of those counterpoints and one that you've mentioned a number of times now that comes from some of these low carb circles relates to low carb adaptation or keto adaptation as it's sometimes referred to, and there's obviously been a lot of discussion and speculation about this topic for a considerable amount of time, but with varying degrees of different definitions around it. So I know in your study, you went about determining that in some objective way, look at this adaptation to a low carbohydrate diet. Can you maybe talk about how you went about that, and maybe even more broadly, to you, what low carb adaptation means, because we see so many definitions around it?

KEVIN HALL: Yeah, I mean, the cynical definition is that if you haven't seen a benefit of the fat diet, you just haven't waited long enough. That's the cynical definition. I wouldn't, you know, I don't think I would go that far. I think that there are clearly adaptations that occur. We know it takes several days for the maximum effect of lowering insulin on lipolysis and ketogenesis to occur. We know that when you do the, for example, we saw in this study, it took about a week for the ketones in the blood to kind of plateau. And we've done previous studies showing that between weeks two, three, and four of a ketogenic diet, ketones are stable. So it doesn't take many weeks to adapt and maximize the ketone levels in your blood, as has been suggested, based on complete fasting

experiments, which is not exactly the same situation, where that does, in fact, if complete fasting takes several weeks for ketones to reach their maximum levels. But that does not happen in ketogenic diet. So we set out with several objective tests to try to say, at least at the end of the two-week period, were people, were there indications, objective indications that people were fat adapted, and one of them was the ketones, like I mentioned, that they were stable over the second week. The second, and they were very high, so beta hydroxybutyrate, on average, during that second weight was 1.8 millimolar, total ketones somewhere, I can't remember, I think it was somewhere between three and four millimolar at the end of the second week. We also observed that people's – we put these folks in respiratory chambers during both weeks to see how their respiratory quotient, which is the ratio of the total carbon dioxide production to oxygen consumption, it's an index of how much fat versus carbs they're burning. So if you're adapted to a very high fat, low carbohydrate diet, that number should be relatively low. And indeed, it was very low, in our case, it was 0.75 or something like that for 24-hour respiratory quotient during the ketogenic diet, and it was something like 0.88 or something like that during the high carbohydrate diet, so a very low respiratory quotient.

We also looked at something which you hear a lot about in the ketogenic diet circles of be aware of taking oral glucose tolerance test after being on this diet, because if you've been fat adapted, you take this test, you're going to become glucose intolerant, and that's something that's well known and people say that's a property of being fat adapted. And indeed, I think that that probably is, because when we did an oral glucose tolerance test, at the end of both of these diets, people did much worse in terms of their glucose tolerance at the end of the ketogenic diet, again, indicating degree of fat adaptation. I don't consider that pathological, I think that that's just an index of

the fact that people have been adapted to this diet for a period of time. They're not used to huge carbohydrate loads, which is exactly what an oral glucose tolerance test is, and therefore when you challenge the body with an oral glucose tolerance test, if you're in a fat adapted state, you will not do very well with that challenge. And so, I think that's an objective piece of evidence that these folks were, in fact, had achieved some significant degree of fat adaptation.

The other thing that's known is that uric acid basically can almost double or it can actually double at the onset of a ketogenic diet; and previous folks have shown that, as you adapt to a ketogenic diet, uric acid levels decline. And in outpatient ketogenic diet studies where people provide all the food, it seems to take about six to eight weeks for uric acid to kind of come, that doesn't quite come back toward all the way to baseline, but it comes to within 20 to 50% higher than baseline. And in our case, it was I think, 30% or 25% higher than baseline, suggesting that they kind of achieve the same level of keto adaptation as an outpatient study for a much longer period. And that might not be too surprising, because in our study, people have absolutely no opportunity to cheat. So in an outpatient study, you might be prolonging that adaptation period with a few cheat days or something like that. So I think that there are several kind of objective estimates that suggest that people had achieved a significant amount of adaptation, but, of course, there's a whole bunch more potential objective things that people could mention that we did not test. So we didn't look at maximum fat oxidation in endurance exercise challenge, that was not part of the study design, and maybe it does take longer to adapt to that sort of challenge, and we don't have any data on that.

DANNY LENNON: With all this said, and like I said, this has been a fantastic addition to the evidence base, and I think, credit to you and your colleagues on an absolutely fantastically done study. So from

here on, what are some of the next steps, I suppose, what are questions that you think maybe were raised either through the study or just more broadly in relation to this concept that you would like to see tested either by your group or by others?

KEVIN HALL: For my view, I mean, what this study does is really provides a way of thinking about the factors in our food environment that influence how many calories we eat, when we're not trying to change our weight, and, in fact, are blinded to our weight changes and various other physiological markers. And we highly suspect that there's been something in our food environment that has changed over the past several decades, that has led to the increased prevalence of obesity. And this kind of study design shows, which I think is really fascinating is that exposing people to these very different and artificial in some sense food environments, because no one has to pay for any of the food, no one has to prepare the food, no one has to generate a meal plan, they just kind of get their meals plopped in front of them, but you can control various aspects of the food that's being served to folks, provides a mechanism of testing to see what aspects of the food environment influence calorie intake. And so, we've actually done two of these experiments now, the one that we just discussed, and a previous one that was published in 2019, where we actually kept the macronutrients constant. So we kept the carbs, the fat, and the protein the same, we kept the sugar the same, we kept the fiber the same, but we actually varied the extent of processing of the foods that were available; in one case, an unprocessed diet; in the other case, an ultra-processed diet.

And so, it was a very similar study design to the one that I just described to you, that was recently published. But in that case, we actually found that one of the diets lead to weight gain and body fat gain and overeating of many hundreds of calories per day, and that was the ultra-processed, by a mechanism that we still

don't understand, because it turns out, again, not accidentally, but the energy density of that ultra-processed diet was the same as the energy density of the ketogenic diet. So it's about two calories per gram. So energy density was the sole factor driving the ultra-processed diets' overconsumption, then why didn't we see it in the low carb ketogenic diet? It suggests there's something else interesting going on. And then similarly, the unprocessed diet, even though it had much higher fat than the low fat plant based diet in the current study, it had the same non-beverage energy density, and yet, in this more recent study, the whole food plant based diet led to much more fat loss than the unprocessed diet. So it suggests that there is some interesting interplay between carbs and fat that's more than just energy density. And so, I think the variety of factors that are kind of going to play a role in determining calorie intake, and what determines weight gain and body fat gain, and again, we're seeing very big stark differences in energy intake between these kind of two, these pairs of diet studies, I think this current paradigm is going to really help us tease out the interplay between these various factors. No one's saying energy density is not important. No one's saying that carbs and insulin are unimportant. No one's saying that eating rate isn't important. No one's – but neither of these factors alone, I think, can explain our observations. And so far, we've done four of these kinds of diets, and only one has led to weight gain and body fat gain, by mechanisms that we still don't understand, and that's this ultra-processed diet that was moderate in both carbs and fat, but had relatively high energy density. But the energy density, I don't think, can explain it, but we're going to design a study to figure that out.

DANNY LENNON: Awesome. And yeah, it's going to be fascinating to see some of this teased apart over the coming years, and I certainly look forward to more work being published from your lab and from others related to this. So with that, Kevin, that kind of brings us towards a close here. For

maybe people who are interested in learning more about the work that you and your colleagues are publishing, or if they want to find you anywhere on social media, or anything like that, where are some places on the internet you'd like to send their attention?

KEVIN HALL: Yeah, so you can always find our work published in PubMed, eventually, PubMed Central will have all of our research published. Our data is available on the Open Science Framework, so you can download the individual data from these subjects if you want to analyze the data in a different way yourself. Please go for it. I'm also on Twitter, and you can link to my Twitter handle and happy to answer questions that people might have.

DANNY LENNON: And I will link to all of that in the show notes for everyone listening. And with that, Kevin, we come to the final question I always end the podcast on, so you've probably got this before, but most times people's answer changes daily, if not weekly, so I will ask you again. 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?

KEVIN HALL: Gosh, so much has changed since the last time you asked me that question.

DANNY LENNON: Right. The whole world is very different.

KEVIN HALL: Exactly. Love each other, do some exercise if you can find time in your life. Try to minimize consumption of ultra-processed foods if you can. And yeah, let's try to treat each other better.

DANNY LENNON: I love it. And with that, Dr. Kevin Hall, thank you so much for your time here today. Thank you so much for the work that you have done and that you continue to do. It's very much appreciated, and I really appreciate you coming and talking to me here.

KEVIN HALL: Thanks, Danny.