Transcript

Danny Lennon: So here we are! A big welcome to the podcast to Dr. Priya Sumithran. Thank you so much for joining me. I'm very excited and I think, as I've mentioned to you, I've read a number of your publications previously and you are involved in an area that I'm very intrigued to learn more about and have had an interest in for quite a considered period of time.

Before I get into any of my questions, maybe we can set some context for people listening. Can you give a brief introduction to your own background, your current work in the field and your current research interests?

Priya Sumithran: Sure. I am a medical doctor. I specialized as an endocrinologist. Then I did a PhD at the end of my endocrinology training, and that was where my interest in obesity.

So I did that really to try and answer the question or, answer a small part of the puzzle of why almost everybody who loses weight puts weight back on over time. And so I did a study that we'll probably talk about later. But so I then started in research. Then I just stayed doing 50/50 seeing patients and doing research for a while.

And then... now shifted to spend more time in research than clinical work. But basically, my clinical work focuses on treatment of obesity in adults and complications of obesity like type two diabetes. And my research all focuses now mostly on. Also treatment of obesity in adults. But elements like, are there certain aspects of treatment that we're overlooking and how do the more successful treatments really work, like weight loss surgery and also, which is a big factor in a lot of places, is that how can we make these really great accessible treatments sorry, great effective treatments, more accessible to people that currently have limited access to them.

Danny Lennon: Fantastic. And that sets the stage for a number of things that I'd really like to dig into. Maybe to start off with, and I think it's something you alluded to in your answer there, that is this important question as to why weight regain almost is the norm as opposed to the exception. And part of that at least, is explained by how humans regulate body mass in general. And so we have these homeostatic regulators of intake and expenditure. And within this is a concept that some people have heard of, but maybe not everyone.

So if you were introducing the concept of this homeostatic regulat, Of body mass in humans to a group of say, medical students for the first time, what's a good way to introduce what we actually mean by body mass

regulation?

Priya Sumithran: I think it's something that we all know really from personal experience.

I think it's something that most of us have personal experience of because. If you think about the fact that the average adult consumes about 1 million calories per year, and most of us maintain a fairly stable body weight for prolonged periods during our adult lives. Even if we were to gain, say, two kilos every five years, that would still indicate that we had matched that intake of a million calories a year with its expenditure, with a precision of around 0.2% over that period of time.

And yet what we are eating. And the activity that we are doing varies quite a lot, most of us from day to day. And while there are some people that are really into their fitness and their tracking, it's clear that most of us aren't

calculating and matching that carefully, and we don't have to put a lot of effort into maintain stable weight if we are at our usual weight. So that indicates that sort of indicates that there is a separate process that we aren't consciously controlling. That is maintaining that sort of stability.

Danny Lennon: So we have this regulation that you said through as I'm sure we'll talk about many different hormones and systems and so on, that allows a really good matching up of intake and expenditure, especially when we zoom out and think about this million calories per year.

That's a really impressive degree of matching up that our body naturally does. Regulates us when to consume, when to stop, when to move around, when to move around less in order to maintain this homeostasis. This opens up the point where much of your research interest comes in of, okay, if we have this ability in humans for this pretty good homeostatic control of intake and expenditure to maintain a certain body weight, what is going on then in a situation where obesity develops? Is that something that some sort of changes lead to obesity pathogenesis? Is it part of obesity developing as a state itself? What is going on when we think of the state of obesity versus this situation we've just outlined?

Priya Sumithran: It's not... It's a really good question. It's not really clear. Whether, obviously, people develop obesity, people put on weight, and so the homeostasis isn't really the only component, but it is clear that it is an important component. And there are other, many other drivers. Food intake and they include hedonic, reward pleasure, social cues the food environment.

And it's also clear that there is, there's been a huge increase in the prevalence of obesity over the last 40 years. And that doesn't indicate that there's been a change in the. You know that homeostasis works, for example, It's almost certainly that it's the environment that's changed so massively during that time that's driven the rise in the prevalence of obesity. But what specific components of the environment? That is, is it, all the things in general, the fact that we're more sedentary, the fact that we don't have to expend as much activity in our jobs or in our lives because many things are automated? Is it the fact that there's more high calorie food around? Is it ultra processed foods? Is it a certain ingredient in the foods? Those things are not clear. But the other thing is that we all, not fall, but if. All people within an obesogenic

environment, not all people are going to be similarly affected by the environment because without a predisposition to obesity, which is largely genetically determined, then the environment can't have that effect on promoting the obesity if you are never going to be prone to the effect of that environment.

Danny Lennon: So to emphasize for people, you've said: we do have this homeostatic regulation of body mass, but of course that's not the only thing that influences our intake and expenditure. We have things outside of that. For example, our environment, our typical behaviors that can in some. Or at least in certain situations, override that. Override that. Yeah. So in, in a classic example of any situation where. Eating even though we're not hungry, right? And we're able to eat more and more calories and then we have this but this environment is exposed to many of us, but where that actually leads to a development of obesity may have be down to genetics, that someone is more predisposed to that environment to lead obesity.

Priya Sumithran: Yeah, exactly. And particularly the degree of the weight gain. because I think if you took a hundred people from the opposite of an biogenic environment and you then put those same a hundred people in a very biogenic environment, everybody would probably gain weight, even the people that were in obesity prone would gain weight, but they may only gain a couple of kilos. Whereas there'd be people who. Much more predisposition to obesity that would gain very much more weight.

Danny Lennon: One of the things that comes up in this area then, when we're thinking about this regulation of body mass, is different models that have been proposed over the years.

People may have heard about body weight set point or body fat set point, settling point theory. More recently I think John Speakman has popularized dual intervention point model with regard to these, and again, proponents for each of them, and there's some interesting debate there. Do you think the current evidence best supports one of those particular models? Or in your mind if it's something different to that, how do you conceptualize model that goes a way to explaining this?

Priya Sumithran: I think, as you said, there is, there's observations that are consistent with each model, but neither the set point nor the settling point

really explains everything that we observe, which is why these hybrid models of which the dual intervention point have come up.

So I think from my interpretation of the bulk of the evidence, given, bearing in mind that there is a lot of conflicting information. It's fairly, I'm pretty convinced that there is a defense of a minimum amount of body mass. What component of body mass that is, is also a matter of debate, but it, I think that the evidence supports that we defend a minimum level of fat mass.

So as our fat stores are depleted there's a response to oppose that. And there is also evidence though it's less consistent, there's evidence that there is an upper limit of weight that's defended. It's not as consistent that's an upper level of fat mass. That may be an upper level of total mass, or it may be another component of mass.

And I think it's reasonably clear that level that's defended is not the same in both direct. So there is a minimum level and there's a maximum level, but it's not a point. So I've always thought of it as a range, and I think for me something like the dual intervention point where there's a lower level and upper level and a range that is not, is, may drift in. Is probably what makes most sense with my interpretation of the evidence.

Danny Lennon: Maybe let's talk a bit about, then we have a situation where obesity is already established and in those situations where we're then attempting to have some degree of weight loss. , And I think it's pretty uncontroversial to say that in a state where someone is living with obesity and we get a certain amount of weight loss, we can measure pretty reliably improvements in health at least in physical health.

What type of thresholds do we see some of those kick-in at? And obviously that maybe differs across different markers, but is there a certain threshold that we see that if we can reliably induce this degree of weight loss, then we can be almost certain that there's gonna be some degree of health improvement?

Priya Sumithran: The benefits of weight loss on weight related complications. start with really small amounts of weight loss. So even three to 5% weight loss will have this is average not within individual, but on average three to 5% weight loss will have start having benefits on prevention of diabetes in

people who don't have diabetes. Reduction in elevated triglycerides, which are a component of the blood fats, reduction in blood pressure improvements in blood glucose control in people who have diabetes. And so those benefits start from really small. Amount of weight loss. But there is no doubt that progressive weight loss has progressive benefits, at least within a, the range of say between five and 25% weight loss.

As people lose more weight within that range, on average, there are greater benefits. So for example, things like fatty liver disease. Sleep apnea, those things probably require about 10% plus weight loss, remission of diabetes in people who have early diabetes and a good residual ability of their pancreas to produce insulin, that takes at least, on average, 10 to 15% weight loss and quality of life improves even with five to 10% weight loss, but overall on average improves more with greater weight loss.

Danny Lennon: Recently there was a nice review, I think it might have been Abd Tahrani (and John Morton) looked at 10% or more of weight loss. And like you said, these number of different outcomes where we see marked improvement. And then we, from that perspective then how do we balance that with what may or may not be doable, Whether it's some debate, right? So we have this distinct thing where certain interventions, so surgery maybe some of the medications we'll talk about later. Or our different thing unto themselves, or we can get that quite reliably if we focus just on lifestyle changes here.

And if people are counseled around diet and physical activity, typically what level of weight loss do we see is. Is possible with many of those interventions in the first place. And we can leave aside the maintenance of that for a moment, but just initially what do we see is possible and does that match up with some of these thresholds that we would ideally like to achieve?

Priya Sumithran: Yeah, that's a really good question and again, I'll preface it by saying that we are talking in averages. And with every intervention for weight management and obesity treatment, whether it's any lifestyle intervention, any medication, any type of surgical intervention, there is a huge range of variability between people in people who respond really well to the treatment and lose a lot of weight and have a really good health improvements and people who will gain weight after any of the interventions.

But on average, if we were talking about standard lifestyle interventions, which would be improved, quality of diet, reduction in calorie intake, and increased physical activity and behavioral modifications, so standard lifestyle intervention. would typically result on average in something like five to 10% weight loss within 12 months, maybe five to 7% within 12 months, but almost invariably as you mentioned that we won't talk about, but we'll not be maintained longer term. And so that on average will fall short of, and, five to 7% is very good for health. And an important point also is that changes in behavior. So if you improve the quality of your diet you increase your physical activity, you improve your sleep, you reduce stress, those sorts of things, even if you don't lose a lot of weight.

You will still improve your health. So it's not all about the weight loss, but the five to 7% weight loss. Say, 5% weight loss is lower than you would. Expect to see some of those health improvements on average that you need a greater amount of weight loss for. And until recently, as you mentioned, we haven't really had much that would be expected to achieve more than 10 to 15% weight loss in the majority of people that used that intervention. So we've had standard lifestyle interventions that might achieve somewhere between 10, 5, 5 and 10% weight loss, and we've had bariatric surgery. Which would be expected on average to achieve somewhere between 20, 25, 30%.

But we haven't really had anything that would reliably and scalably achieve the weight loss in the in between range. And so most clinical guidelines for the management of obesity and weight related complications have focused on recommending weight loss of around 5%, not because. That's the optimal amount of weight loss, but because that was all that was considered achievable enough to be recommended in clinical practice.

Danny Lennon: Yeah, that's a really important point because there's that conundrum that you bring up for clinical practice of let's say. pick an arbitrary number, 10% or more of weight loss can lead to these list of benefits. But if there is some degree of probability that on average, a decent amount of people undergoing a certain weight loss intervention may not achieve that, but we know that.

Even at five, six, 7%, they're getting some benefit, even the change in their lifestyle without weight loss or causing some health benefit. So are we to disregard those as a success, just because we haven't reached this point, and

more, probably more importantly, for the patient or the client, they themselves, do they frame it then as a failure to have meet an initial goal setting Yeah. Of a certain point. From a clinical perspective, how do you think clinicians can go about discussing this with patients initially when they're thinking of, Okay, here's our goal or our plan of action, What type of nuances are there to having that patient discussion?

Priya Sumithran: Goals are really important. But we actually had a debate about this during the conference (International Congress of Obesity) , that one of the sessions at the conference was about targets. Targets like goals for intervention and are they unrealistic? And what are the ethics of setting them really? So I think a weight loss target can never be the only goal because it's far more important to understand the why. Why you needing to lose weight? Why you wanting to lose weight? What will you be wanting to achieve out of the weight? Because those things might be achievable even without that target. So I think it's not bad to have targets on their own. For example, with all other chronic diseases, we have particular targets.

We have targets for blood pressure, we have targets for blood glucose control in people with diabetes and for some people, we understand that they're unrealistic or that they might never achieve those targets, but any progress towards those targets is still valuable. But I think with weight goals it's important not to just set a goal for the sake of getting to a particular number.

And I think something that a lot of people who are trying to reduce their. Have in mind because they've heard it either explicitly or they've understood it implicitly, is that they need to get to a normal weight range, meaning a body mass index of 25 or less, 20 to 25, and that is, Absolutely should never be the target.

For the sake of just getting to a body mass index of 25, there's no sense in that for the individual because that body mass index of 25, because it's called a healthy weight range, a lot of people have a perception that they're not going to be healthy or that they're not gonna be considered healthy unless they reach that. But within individuals, there's no relationship necessarily between a body mass index of 25 and their actual health.

Danny Lennon: One of the things that comes up when you say that there's a really nice illustration in some of Roy Taylor's work in the UK on the diabetes

remission, and sure you can see the averages for the group and changing of bmi, but if you look at individual data points, you have people that lose a substantial amount body weight based on that intervention. Very low calorie intake, but they're, the weight they're finishing at is still within a range would classify as obesity, either class one, class two, But those people have now put their diabetes into remission. Yeah. So to think that they have failed to reach a BMI of 25 is strange.

Priya Sumithran: Right. It's, Yeah. And his, his work is really interesting, not just for that, but actually at the opposite end to show. There are plenty of people whose body mass index is below 25, even before they lost weight, who had metabolic complications such as diabetes and who will still benefit from weight loss, who will still have remission of their diabetes with weight loss, even if their body mass index was within the healthy weight range.

It's more about the personal on a personal individual level, what effect that. Has on you, regardless of what your actual body mass index is cause Yeah. At the other end, as you say, even after bariatric surgery, which we know has huge sustained health benefits with an average weight loss of 30% of starting weight, most people who have great outcomes from bariatric surgery, We'll still have a body mass index, well above 25, usually well above 30, but who have excellent health.

Danny Lennon: Yeah. So we're not using this one number as a way of defining health or unhealthy, It's more this kind of population screening tool. Yes. One of the things that we've touched on a couple of times has been this, on average a failure of weight loss maintenance, which is pretty consistent along much of the large behavioral programs at least where you see over a period of time, a considerable number of participants regain a certain amount of weight differing between those people. Of course, of how much is regained back. But certainly there's a decent amount of weight regain over the, at least the next couple of years for some of these longer term studies.

And so given that we're this, what I suppose is where we get this emerge, of people then questioning is it worth pursuing weight loss in the first place given this on average, maybe a lack of ability to maintain? Are we better focusing on some of the elements you've already mentioned of we can improve someone's health through these other behaviors?

And so this obviously, it can go too far in either direction because clearly there's lots of examples where people lose consider amount of weight and it transforms their health and their life. So what it probably comes down to is then how do we effectively know how an intervention is gonna work for this individual versus someone else?

And I think, at least from what I'm aware of, one of the gaps seems to be, at least for practitioners and clinicians, is a validated screening tool of knowing exactly who it's contraindicated for and who should go on intervention right now. Where are we in relation to actually having something like that develop?

How far off do you think that could be? How difficult a job probably would that be to come up with? Or any other thoughts you just have on that general idea of how do we effectively screen for if weight loss is useful or contraindicated for this patient.

Priya Sumithran: Yeah, I think the key question to me is not so much is it useful or contraindicated, but is really particularly as there is a growing number of interventions that could potentially be used either alone or in combination.

The key questions are who should lose weight and who should focus on health improvement, but not weight loss, but also, , given that there are going to be a lot of people who are gonna benefit from weight loss, which intervention is most likely given that there's so much inter individual variability in the results of all interventions, which intervention is most likely to be the most suitable for that person. ? And at the moment we don't have good ways of doing that really. We do have contraindications, so there are, there and we can to some degree, tailor benefits to the mechanism of action of certain medications,certain surgeries, for example if somebody has diabetes, you may be more likely use a certain type of drug.

If somebody has high blood pressure or takes certain medications for psychiatric illnesses, you may be more likely to avoid using certain types of medications. So we do it. With, based on those sorts of things. But what we would, what we ideally would be able to do, which we can't currently do, is assess the person for what is really underlying the difficulty that you are having in reducing your weight or improving your health, and which

intervention is going to, which intervention or combination of interventions is going to be the best at addressing that? We don't really have that at the moment. The best predictor of weight loss is early weight loss, meaning your. You start the intervention, you wait a couple of months and then if it's not working out, you may change it, but it would be more useful to, to know before you started the intervention if that wasn't the right one. We don't have that at the moment,

Danny Lennon: So we're seeing that within any intervention, the people who lose the greatest proportion early on in that intervention have the greatest likelihood of maintenance long term. Yes. One of the interesting things that comes up with this is, okay, even in situations where someone has, let's say they do lose a substantial amount of body weight and some is regained over time, at what point we call that a success or failure, and that's probably bad terminology, but in, in a kind of literal sense, what we determine. So for example, if someone regains all the weight, they lost back, that's probably not a beneficial outcome. Versus if they gained a very small amount back, it may be inconsequential or they might still have clinically meaningful benefit from it. And so do we have a certain, do we have any guidelines around what is still considered to be successful maintenance, per se? If someone loses 10 or 15% of their body weight and they regain some back, but not all, at what point do we still consider that? That's still effective maintenance.

Priya Sumithran: There aren't hard definitions that I know of other than in the bariatric surgery world has definitions for what is expected and what is considered insufficient weight loss, for example. But in, in terms of non-surgical interventions, it would be considered, for example, that if you maintained a weight in the long term that was more than 5% below the way you started that would be considered reasonably successful. More than 5%. More than 10%, that would be very successful. But it doesn't tell you if you may have lost 50% and then regained just to maintain that 10%. And I don't think it's really particularly meaningful really, because what is more important is what were you looking for from the weight loss?

Have you achieved that? And is that sustained? So really, If your, say for example, if your diabetes was well controlled and it's still well controlled down the track, it matters. It perhaps matters a little bit less, whether you've regained a bit or you haven't regained, but it's likely that as you regain most of the complications associated with the weight, that improved with the

weight loss do tend to recur. So that's why maintenance is important. It's because the health benefits of the weight loss are also lost with the regain.

Danny Lennon: But I like the way you phrase it, that the weight is really just in that case a proxy for more important indicators. So like you say, if there is some weight regain that what percentage was regained is inconsequential relative to what, Was there change in hemoglobin a1c or what was there change in LDL cholesterol or any of other things that we care about. Blood pressure, for example,

Priya Sumithran: Those things may not improve, but they may be as well controlled using fewer medications, for example. And if that's still the case down the track does it really matter that you know what the weight has done?

Danny Lennon: A great point. That's it's a way of framing what are we gonna term a success for this person's life? Yeah. I really like that. One of the things when it comes to interventions first when we look at dietary intervention, which is a first thought for a lot of people the thought that diets are bound to fail or all diets fail has become common, but that really, to me lacks the context of what we're talking about, right?

Whether someone goes on a diet that they've Googled "weight loss diet" and just followed the first thing that popped up on Google, versus if they are working with weekly interaction with a registered dietician that. Clinic may have a psychologist on board, maybe they have other supports available to them and all other changes within their lifestyle to call both those a diet intervention and therefore think we can evaluate them the same way seems a bit odd. And so I think this speaks to. What you said, what is that person having difficulty with either achieving weight loss or maintaining it, and then what are those supports that they may need around them? Because for one person it might be just education for another person that might be nothing at all.

It might be psychologically related, and so they're. Intervention or their treatment will look very different. And so yeah. I find it very strange that we can name one thing is just, Oh, diets do our don't work. Yeah. To get to some of the breakthrough that's been happening in more recent years, that there's of course a lot of real interest and further right now for good reason is around

some of the drugs that have been came on board, some of the GLP one agonists in particular. Can you maybe just introduce people listening to some of those recent drugs that started being rolled out? Some of the early results that have shown so much promise, or I've got people so excited. And then in your mind, the kind of potential implications of the current evidence so far.

Priya Sumithran: When we eat or consume nutrients, our gut produces a whole lot of hormones in response to what it is that we've consumed. And those hormones the signals from those hormones do several things. So from various parts of the gut and the pancreas, there are hormones that are produced that signal that we've. Eaten something and so we feel full that our body has taken in glucose. And so we need to produce some extra insulin from the pancreas to keep our blood glucose levels stable and to slow down our gastric emptying.

And so GLP one is a hormone that our gut normally produces that helps us feel full, slows down the gastric emptying a little bit, and stimulates the pancreas to produce some extra insulin if our blood glucose levels are getting elevated. In people with diabetes type two diabetes, that response is a little bit impaired and there are a large number of these gut hormones. So GLP one is one of them. G I P is one of them. Amylin is a pancreatic hormone. That's one of them. And together, all of these hormones have various roles in either fullness or glucose metabolism or other actions in the body. So the newest. There are many approaches to medications that are in the works, but some of the newest ones that have received a lot of attention that are looking like they're going to be very effective are ones that are based on these gut hormones.

The GLP one receptor agonists have been on the market several. Ones for around 20 years. And I will say that actually yes, they're based on our own hor hormone GLP one, but our own endogenous GLP one is very quickly broken down. And so it doesn't last very long in the circulation. All of these GLP one medications that we have in clinical use are, have been made to prolong the action of GLP one.

And so the latest versions are once a week. We started off with ones that you had to take twice a day and then once a day and then once a week. They were they've been on the market for many years for the treatment of diabetes because they are great at treating diabetes, but they, as we talked about

earlier, also help reduce hunger, help people feel fuller with small meals and are a medic, a treatment for diabetes that helps reduce weight. Whereas previously there were treatments for diabetes that often are weight gaining and. Because they reduce weight. These medications have now started being investigated for the treatment of obesity and weight management.

And so as an example if we talk about Semaglutide, which is the most recent GLP one receptor agonist that has been marketed for treatment of obesity or long term weight management that in people without diabetes, because for all medications, people without diabetes tend to lose. More weight than people with diabetes.

So when they're tested for the management of weight in people without diabetes a medication like semaglutide at the dose that's used for weight management would result on average in about 15% weight loss, 12 to 15%. And to put that into context, the previous generation of medications that we've had to date resulting on average about five to 6% weight loss. There is another medication called Eptide, which is a dual GLP one and g i P agonist, and that is also being think it's available in the US for the treatment of diabetes at the moment, but it's also being studied for weight management in people without diabetes. It's not available in Australia.

And that is in one study that they've published for obesity treatment in people without diabetes, that at the higher doses results in weight loss of around 20%. There are responders and non-responders, but on average the weight loss is around two to three times greater mean weight loss compared with the medications we've had to date.

Danny Lennon: And this is a lifelong treatment?

Priya Sumithran: That's the question, right? So there are no long term studies of any of these. Medications, and there is a lot of resistance to the idea of using weight management medications in the long term because by far the most common question that you get asked is how long do I need to take it for?

But if you think about, you know what the physiology is, it's like any other chronic disease, you wouldn't expect to treat it with a short term treatment. . So I think at the moment we're in a difficult position because there is good

evidence that if when you stop medication that's been used for weight management, people regain weight.

So there is no medication that we have at the moment that you can use for a period of time and then stop it and expect it to keep working. So it is gonna be it. Any treatment is gonna need to be a long term treatment. Yes. But the problem at the moment is that we have no long term data of safety efficacy and you know how you would really use it to optimize the health benefits,

Danny Lennon: Given that the length of studies we do have seems to show this is incredibly effective, particularly for something where we have had a failure of many other types of interventions and has for the short term a pretty good safety profile. But like you said, this long term issue is more unknown. What have been some of the hypotheses or potential concerns that researchers and physicians have about it in the long term of that, we still need to get this longer term safety data in case of potential harm. Are there any particular concerns that have been proposed?

Priya Sumithran: The history of medication for obesity? If you look over the, over the last century, Is really characterized by the huge number of medications that has made it to the market and then had to be withdrawn because of side effects.

And so obesity medications have this, strike this fear into people, I guess because we are used to the medications that we've had to date that have looked promising, come onto the market and then been withdrawn because of really unanticipated unanticipated side effects in some cases.

So in some cases, the side effects, aren't so surprising because older agents that were around, say between, the second half of the 20 20th century often were based on stimulating, stimulants or stimulating the sympathetic activity. And They had particular side effects on high blood pressure or on heart valves, for example, or on cardiovascular risks.

So that's not entirely surprising. But then there are a lot of medications that have come out and the problem with the areas that in the brain, That they often work on to suppress appetite. Similar areas that are involved in mood, for example. There are some that have had psychiatric side effects that have needed to be withdrawn.

The most recently, withdrawn one, one that we never had in Australia or Europe, but that was approved in the. Which was Locaserin, which was withdrawn because of an unexpected increase in cancer risk, and that only happened in the last couple of years. So we do have this. Reasonably legitimate fear that so many medications have come out and so many have had to be removed.

But I think it is an, and that's something that we do have to bear in mind and we really do have to look carefully at the long term safety data, but I think it is reassuring that the way that the current generation of, at least these gut hormone based agents work, you wouldn't. Expect those types of side effects, because they work in a different way than those older agents did, but we will have to wait and see.

Danny Lennon: Are you quite optimistic on the future direction of treatments? If we think of the progress that's been made in some of these drugs? But obviously that innovation in other drug development will continue, presumably, and also other technological interventions, whether that's gene editing or otherwise that feasibly could happen in the future, it seems like that is the route where we're starting to see with the example we just gave of at least the emergence of real meaningful differences that possibly me be maintained. That we've have no other real answer for as of yet for obesity. So do you think the the answer to our best answer for medicine, so to speak going forward, is going to come through more innovation in relation to medications or other technological in innovations?

Priya Sumithran: Yeah, I am optimistic that I think certainly over the last few. There's really been not just a small incremental progress, but a really big step forward in what is being achieved with not, I not just weight loss, because as we've talked about, the weight loss itself is not the most important thing, but the weight benefits, the health benefits and the magnitude of that compared with the previous treatments and also the lack of certain types of side effects that plagued older medications. I do think this is a time to finally be optimistic for what the future holds and I think this is really just the beginning because if you, there is a huge number of medications that are apparently being investigated that are in earlier stages of testing. And not all of them will be successful, but there's definitely a increase in the pipeline for what might be possible.

Danny Lennon: So with any thing that we've discussed so far, before we wrap up, I really love to hear your thoughts on future directions of research and in particular, is there any one or two big research questions that you would be particularly wanting to see an answer to over the next, let's say, five years, for example, that it could be from your group or from others outside. What is a, an interesting research question that you think so far hasn't been answered, that hopefully upcoming research could help shed some light on at least?

Priya Sumithran: This wouldn't be a thing for any budding researcher. this is something that pharmaceutical industry will be doing, but I think it will be really good to see some hard cardiovascular benefits of non-surgical weight management. So at the moment, we know that it improves. Health conditions, it improves quality of life, it improves cardiovascular risk factors, but we don't have any, There's no medication trial that has really shown an improvement in mortality associated with weight, and that is something that is being studied and I'm really looking forward to seeing those results.

Because I think that will be a really important milestone in the field to, to show that sort of benefit can be achieved. , I think what we touched on before in terms of working out who really needs an intervention for weight who doesn't, who can improve their health in other way, who doesn't need to worry about it at all, and working out then within people in whom you, and they have decided that an intervention is necessary. Tailoring the right intervention to the right person in a, in a more personalized way. That would be a good thing to be able to do. All the things I'm suggesting are about these particular treatments, because this is, something I've been thinking about lately, which, by no means is this the only important area of what needs to be studied in obesity. In fact, the most important thing I think, really does need to be studied is how effectively to prevent the development of obesity and poor health in the population. But within the treatment realm also, how we can use. How we can use these treatments in combination to really optimal effect.

Danny Lennon: Yeah. It's interesting that difference between the prevention, the treatment that you bring up always reminds me of my own nihilism and optimism on different ends that I'm tend to be more pessimistic about the direction at least we've been going so far with degree of prevention, whereas you're seeing so much now success on the treatment side here in certain levels,

Priya Sumithran: But it's been so long in coming. So much invested in. Or so much, talk about prevention and invested in prevention, we really need, Yeah, I think if we could really find the most effective strategies for prevention and then yeah, as you say, the will do, implement them because they aren't going to be easy.

And some of them, I think some of the things are going to be legislative things that aren't gonna be popular with everyone it's not just the political will, but it's public acceptance of what is actually needed. There's a lot to do there.

Danny Lennon: There's a lot of it that be goes beyond evidence, which is the tricky thing. So before I get to the final question, where can people find you on the internet if they wanna either find you on social media or follow some of your group's work, et cetera, where are some places you might send their attention to?

Priya Sumithran: I'm pretty social media. I don't really have a big presence at

Danny Lennon: A smart move. I think you're doing a good job!

Priya Sumithran: I do have a Twitter, but I don't use it!

Danny Lennon: What we'll do is we'll pick out some of the most relevant publications to this particular conversation, and I'll link to those papers directly in the show notes. So for anyone listening, you can go and check out those particular publications. And with that Dr. Sumithran, that brings us to the very final question that I always end the podcast on, but 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?

Priya Sumithran: Do something that brings you joy.

Danny Lennon: I love it. With that, Dr. Priya Sumithran, thank you so much for coming to talk to me today for giving up your. And then more importantly for the work you do and that you've put into the field. It's very much appreciated and it's been an honor to be able to talk to you.

Priya Sumithran: Thanks so much for having me.