Transcript

Danny Lennon: So, we're gonna start diving through some questions. I think these have been submitted by our Premium subscribers. We got a really good batch of questions today, so we've narrowed them down to about nine or ten so hopefully we're gonna try and get through all of these. So with that, let's maybe take the first one.

And let's start with this question from Maya Robinson who says:

"Hi guys, I'm really keen to hear your thoughts on something that's been on my mind for a while. Do you feel that there is hope or an effective way forward for obesity rates to come down based on your response? Why or why not?"

So maybe I'll keep that to you, Alan, to start as based on your thoughts here, or what do you think possible for obesity rates to drop? If so, why? And if not, why not?

Alan Flanagan: I like to be the voice of optimism array of light in an otherwise dark world. Now I think that when we tend to focus on this question we inevitably are thinking about the idea that an individual, and then we could scale up to the population, some intervention that can tip the balance towards a population wide reduction in adiposity.

Right? And when we think about this question, I think ultimately we're thinking about it through the lens of the ultimate director of adiposity, which is energy balance, right? And so there's this conceptual idea that we can shift energy balance, and that can bring a population wide reduction in incidence of and rates of obesity.

And the problem is that uncouples the consideration for how that would be achieved from the factors driving it in the first place. And it, then uncouples the consideration for what the most effective strategies would be if we acknowledge what those kind of main drivers are. so my answer ultimately is going to be no. I think it is possible, but I'll explain why I don't think that possibility is going to come to any kind of fruition. So the reality, if we look at the factors driving it in the population, we know that it will scale along socioeconomic lines. We know that people will be at greater risk of obesity in lower strata of socioeconomic status. As social deprivation increases, obesity rates will pretty much... we see this linear increase. And that's driven then by a constellation of factors that are influencing, not just adiposity, but just health people's access to health. Ranges then in this kind of consideration way beyond just energy balance, right?

It's factors like housing and the adequacy of housing. It's obviously net income. It's food security, which if we're talking about the UK population right now, we're literally on the precipice and about to fall off that precipice of enormous levels of food insecurity, sweeping across the population with this "cost of living crisis", which really is a poverty crisis.

And we know that in order to make any sort of meaningful dent in this landscape, that we require intervention at the top line level, at the level of industry, that intervention needs to be supported by the government. And if you're in a country like the UK, they're literally about to scrap every single intervention that's targeting population wide obesity rates, including marketing, advertising restrictions, literally everything.

So industry is now going to be totally unfettered in its capacity to use everything at its disposal, to get people to consume the worst possible quality diets in ways that we know in terms of ultra process food, precipitate excess energy intake and otherwise. So it is possible were you to have an administration that had the appetite to bring about the types of interventions that could make a change in the food environment and the food supply.

And in the absence of that, I don't see anything changing. So although conceptually, we could say yes, if you really had strict advertising and marketing restrictions, targeting children, if you had more taxes than just a

sugar tax, for example, if you had taxes that maybe targeted the energy content of foods or the fat content of foods, if you had cap and trade approaches, which some people have suggested to force competition between industry to get quote unquote, their emissions in terms of energy and nutrients of concern down, all of this stuff requires a political capital and it requires inter upstream rather than downstream. And currently our focuses are all downstream at the level of the individual. And so as long as our focus remains there, as long as any available policy remains there, I don't think that this is going to be a landscape that changes anytime soon and probably gets worse.

Danny Lennon: I have some similar thoughts when I saw this question initially because I did want us to maybe try and avoid complete nihilism out the gate, like you suggest, I tried to think, well, what areas do people tend to point to as potential optimism in this area. And most of it tends to be around obesity treatment rather than prevention, I would say.

Yeah. So we're seeing the, these highly encouraging breakthroughs in various drugs or weekly injections, which are seeing these phenomenal results. And along that line of thinking one could make the case: "well, we can continue to see these roll out more in clinical practice. We can see development of more of these types of drugs, or we could see even bigger innovations in technology and medication or around like gene editing" or whatever case may be, far into the future that could potentially be used as a treatment.

But of course, that doesn't go to the fact of the kind of prevention piece. And so while the optimism there could be around, these are things that feasibly could make a big impact and are shown to be very successful and efficacious thus far, when we look at how we actually changed it on a population level, you noted exactly something we've talked about on this podcast before that it would really need to probably come from a top down level, addressing the food environment. And unfortunately we have in a lot of places, just zero appetite from governments to do those. And in certain instances, like you noted with the example of the UK, you're actually currently seeing probably the opposite of that.

And so on, on that side, you would have to be quite worried about, well, what kind of landscape are we gonna see in terms of this food environment and how that's gonna play into driving obesity prevalence? Factored in on top of not only the food environment, but many of these socioeconomic and social issues that, that you've just discussed.

So, I mean, feasibly we could see changes in food supply over time that come from innovation or technology or regulation. But whether that addresses the issues related to obesity of just overall consumption, I'm not as, as convinced people could say like on a health basis. Sure. You could see changes in.

Let's say meat alternatives now that end up being actually something that tastes and has a texture exactly. Like meat, but you have less saturated fat. And could this end up being, getting to the point where there's an acceptability in the population where more people consume it. Sure. But we're probably even at that point looking at well, how many people and also we're looking at outcomes more like cardiovascular disease as opposed to obesity, I think with that.

So yeah. Ultimately I share the kind of overall pessimism around whether most societies will be able to take the steps necessary to do that.

Alan Flanagan: If we even rephrase the question in a way, I think that becomes instructive. If we think about obesity rates in industrialized countries as almost a proxy for poverty, We could reframe the question of: "do we see poverty rates declining anytime soon?"

And then that would actually get us thinking differently about what kind of policies would reduce policy would reduce poverty levels in a population. And that's unfortunately where we see certainly in countries like Ireland and the UK and the states less so in other European countries. There's even, evidence that some of the social democracies we've tended to prioritize over, the years as a good example of a positive social model, shift more to market neoliberalism. When we have that kind of model, that very much is an emphasis on individual responsibility and otherwise, and you see really ineffective approaches to dealing with poverty across the board, and you see ideological resistance to what could be effective, then it becomes very difficult to see how we navigate around that.

Danny Lennon: Let's move on to another one. This one comes in from Gabriel who asks:

"In this field, it seems like so many of us have had positions we've held very seriously that we now see as poorly supported by research, or just have a significant paradigm change. Listening to some of the quack asylum episodes, I realize that while you might not ever considered them as references, they almost by default were connected to some degree, to our spheres of influence in the past; colleagues of colleagues, references used by colleagues, et cetera. It would be great to hear you banter and look back on how your views have evolved over

the years, review how you've evolved your thinking about certain pillars of your nutrition epistemology and more."

So's it's two questions in itself there of like how our views have changed and then our way of thinking about that. So, whichever way around you want to take that, do you have any kind of initial thoughts?

Alan Flanagan: Yeah, I think, it's funny. I mean, I think I've spoken about this maybe in, in various kind of channels before, when I started getting interested, first of all, in, in nutrition and kind of the health stuff the angle that I first went at this down from a kind of health perspective was very much the kind of paleo low carb sphere. In fact, the first book I ever read on nutrition was literally entitled paleolithic nutrition. It was written by an academic But, it very much had that kind of more Lauren corinees view of, we, it wasn't entirely committed to that, it very much portrayed what we ate in a certain way.

It didn't glorify saturated fat, necessarily. It very much made the case that high levels of sat fat, even in indigenous cultures probably clogging the arteries via increased LDL. But it was making that case for, we wouldn't have eaten a lot of carbohydrate. We wouldn't have eaten a lot of starch.

We would've had a more kind of meat and animal source food source based type of diet. It. And that kind of self-directed, as it tends to, when you're at that point where you don't have enough domain specific knowledge, or even more of the critical thinking faculties related to science, you tend to then use whatever you've discovered there as as a platform on to something else related that tends to now confirm what you've just been reading.

So I would say that like my early interest and my early forays into this stuff were very much more amenable to any sort of information from the kind of. Low carb. We were wrong about sat fat. I definitely, I went into my MSc based on my own reading to that point, very much having swallowed the Siri-Tarino meta analysis and yeah, and very much on that kind of side of the fence.

And even that influenced my dietary habits at the time. Like I considered a banana being a bit cheeky, carbohydrate intake. And it's interesting. I look, I think there's in terms of how does nutrition epistemology evolve? I genuinely believe across a range of disciplines that there's almost little to no substitute for formal education.

In a world where we increasingly see and certainly the problem with nutrition and the conversation, right, is we have these kind of, "I did my research" self-

proclaimed experts. People that essentially see being self taught as almost it's lionized now. Someone who did their own learning like a Max Lugavare figure is more prized and is more assumed to be correct, because they did their own research and learning rather than an actual expert in the area.

And it's a really weird place from an epistemology standpoint that we've walked ourselves through as a society probably heavily influenced by social media, and. I had the benefit of, I think always appreciating formal education. And so, yeah, at least I was open during my masters to being disabused as I, as my learning of evidence and science grew.

And as my exposure at Surrey to some... professor Bruce Griffin in particular, who really like, was instrumental in helping me see why these meta analyses were flawed, the saturated fat ones, for example. And so you come in, you come away with... I think there's two ways we can conceptualize this one is like raw knowledge.

So I had done a pretty voracious amount of reading prior to my masters, but I would call that knowledge without context. And then there's, you start to learn certain skills in terms of understanding scientific literacy in a general sense. And then also the domain specific scientific literacy factors that need to be considered for your own research area.

And when those two marry, then you start to get context on what it is that you're reading. And so I think for me, that understanding was instrumental in being able for me to move away from those original rabbit holes that I had gone down and accept them as flawed in many ways. But from an epistemic standpoint, I think I was also fortunate with the legal background in that law is obviously a field heavily influenced by its own epistemology. And I started to be able to almost at the outset without realizing it to, to look at nutrition and to start to consider where does our evidence come from? If we have a study and we say, this is evidence of X, how have we arrived at those conclusions?

And that's a very legal way of thinking. It's not just enough to say I have evidence. You have to actually prove the Providence of that evidence and where it comes from. So I think I was fortunate in that sense as well, which heavily influenced me starting to look at nutrition more for what makes this field unique, what issues are there, methodologically.

And that, that starts to very much inform my own kind of epistemology about the subject. Then over time.

Danny Lennon: It's interesting as you were giving the answer, how many of those things tallied up were some of the notes I'd made when I was looking at this question. Of initially how I started out again very much in a similar vein of reading in and around the paleo/ low -carb community that ends up then expanding naturally into more of the low carb, high fat stuff.

Even having note here that literally references the Siri-Tarino meta analysis. Think it was 2010 that came out. And so, yeah, in the next two, three years, the kind of internet just went crazy for this thing. And all those arguments around why low carbohydrate may be beneficial for health, for body composition.

Why saturated fat doesn't need to be worried about they all seemed reasonable when you're exposed to the way they were portrayed. And of course the same thing with anything paleo or ancestral related is it seems intuitive. And I think that's why it garners so much support in the same way that gluten was another one for me from the Paleo sphere as well, of you nocebo yourself into thinking you have a gluten sensitivity because you're hearing so much reinforcement from a whole community of people who say the same thing. And of course, then you start taking out and say "oh, I don't feel too bad." and then you have something that contains gluten and say "oh, is that something?" And then you realize eventually this was all nonsense that I genuinely believe these things were like were happening. And in a very much, same way to you. I think that the biggest thing that I've came to learn when I try to think, well, well, what way, how am I now better able to look at information and as opposed to back then, one is obviously just an understanding of nutrition, science principles, more broadly, which you point to of just trying to be as scientifically literate as one can, and then just a greater degree of appreciation for domain specific expertise. Yes. And I think this is the thing that you essentially touched on with the example of people who are revered for being outside of the field and giving their input. And. These can be incredibly smart people, right? That have expertise in all sorts of different domains.

They can even be scientifically literate in some of these fields. And can they know the anatomy of a research paper, for example. Yeah. But that doesn't translate to understanding a whole body of a specific field because there, there are so many things that they're unaware of and that you can only learn that through years and years of exposure and many of the questions they think they are stumbling upon or getting answers to that no one has thought about are in fact questions that a lot of the main researchers in that field have thought about and probably have got answers to many times over the years and have looked into and just found, well, no, it's like, it's not correct what you're saying.

And I think that, that domain specific expertise is often. Nowadays portrayed as a negative, right? Oh, these people are too inside their own field. It's all just reinforced or you're brainwashed by dietetics or the nutrition fucking hierarchy or whatever it is. And it's just that is not the case, right?

Alan Flanagan: No, it's bullshit. Yeah. Kinda like "Tim biohacker"... remember, I was showing you those posts in Australia. Like this dude being like: "oh, the system's brainwashed you". His whole take was I have these stances because I'm in the field, he said: "oh, you've got a PhD. You obviously just you're towing the party line". It was like, what? You're just a bro, yeah.

Danny Lennon: And it's so fascinating because I start thinking about this with other fields now where I don't have expertise. You think, well, so many things that you think, or you come across as popular information.

These areas is probably likely incorrect, whether that's psychology or philosophy or whatever, and someone could come and think they have a really good take on something and you only get shown up when you meet someone who really knows what they're talking really about really.

And that is the difference between people who stumble into a field and spend a couple of weeks reading up on a certain area and sure. They could read a lot of research, but a few weeks is nothing compared to people who are literally embedded in this research for years and decades.

Alan Flanagan: Yeah. I think there's, I think there's a timing component as well, which I'm interested because... when did you finish your masters?

Danny Lennon: That would've been in late

Alan Flanagan: 2013.

Okay. Because, so this is the interesting thing to me because the fact that you found that say paleo stuff, because. I'd say from about 2007, eight onwards is when that really exploded as a paradigm. And you had all of these blogs getting, Mark's Daily Apple, and all this kind of stuff got going.

And at the time that was the big movement, as far as people "asking questions". And so I could conceive for example, that if we only started becoming interested in nutrition in 2017, that it could have been something completely different, it could have been a more of the kind of extreme plant based stuff that, that, that attracts, someone in the first place.

So I think that whatever is, I think we discount the role of a lot of the chance factors, maybe sometimes in this, that actually, I think that my interest in that, because I happened to get interested in this stuff around oh 8 0 9 and at the time, I happened to that. That was the stuff that happened to be big.

And the other big thing at the time independent of the like paleo stuff. And I went through a phase like you, you brought up the gluten thing. I was pretty hardcore about thinking gluten and dairy were going to do me serious harm. and I was militant about dairy is not supposed to be consumed by humans for a couple of years.

But what's interesting is the other thing that I was like hook line and sinker for was lean gains was the intermittent fasting 16, eight. And I stumbled across Martin Berkhans blog in about oh 9 0 10. And at the time was like six meals a day, every two hour, blah, blah, blah. And this blew my head off, this was revelatory, and I did that in a kind of paleo context to a T, I did everything that he said, do a T.

So it's funny in that sense that I was almost combining two fads in a sense that, I mean, look, intermittent fasting is more of a way of eating, but yeah, I was doing both,

Danny Lennon: I was doing the same. I remember before I did my master's, I was a teacher for a year and that year I would go and train before school.

So I used to train in the University of Limerick gym. because the school was nearby. Would train there like six 30 in the morning and only have BCAAs. And then wait until lunch time to eat. Yeah. Yeah. On the base of that. Yeah. The timing thing is really interesting to consider. At least where I got, I think maybe where I've got the first initial recommendations was this kind of coincided with the explosion and popularity of CrossFit in Ireland, I think around that time and was taking over the kind of fitness scene around that time.

And so you were getting so many recommendations around paleo based nutrition because it had that close tie with CrossFit. Yeah. And then, so that was what people were recommending and you look into it and the same thing. And I've used this example before of like the luck component that you bring up of people who end up getting lucky that the first exposure they had to like thinking about nutrition was they found Eric Helms, for example.

Yes. And just follow this. And that was just luck, right. It wasn't that they knew better than someone who falls for low carb stuff. So yeah the timing thing is. It is very real. Yeah.

Alan Flanagan: Yeah. And that was it. I mean, I remember we mentioned this on the episode we did with Eric and Omar, but, Underground Wellness was like one of the first, probably the, I dunno how I came across it, but it was the first health podcast that I ever came across.

I didn't listen to anything remotely related to health as a podcast and podcast was obviously emerging at that time as a medium But if I did listen to something, it was always like, the history of ancient Rome or something like that, and and so, and what was interesting about that podcast as you remember, is it wasn't ever just like nutrition, like he interviewed some really out there, people like on a range of like weird shit, like his episodes with Paul Chek, I think back to now.

And I'm like that, that's, that dude's insane. Paul Chek is insane, like insane, but and so, so much of what I did with my health and my diet and my general day to day wellbeing, I just licked straight off that podcast. I would listen to an episode and someone was like, so thank God, I'm not vulnerable now.

Cause I could be out there sticking my ass towards the sun, but yeah I literally would adopt a practice almost overnight. From listening to something in an episode like this and being like, oh my God, I need to do this. So yeah, I think there's a logic to be said for just the basic critical thinking.

Danny Lennon: Yeah. And it's there is that luck of like how you get out of it and who you get exposed to of, like you said, of. The people you were exposed to, obviously with the masters. And I had a very much similar thing of... even some residual things around the kind of paleo narratives I still had going into that master's program.

Remember talking to in emailing some of my lectures one in particular, Tony Sheehy, who was in UCC about some of the epidemiology stuff, and then around like some of these paleo populations. And it was just really useful to see how someone handles that in a way where it's a kind of respectful dialogue and actually showing you things that you might not have been aware of.

And then also I think it was around, I think it was 2013 could have been thousand 12, but I think it's 2013. I actually went to an Alan Aragon seminar in London. And that was the first time I'd been I just remember coming out that

was like, this is unbelievable. I'd never seen actually someone talk about actual studies in this particular way.

because up to that point, I've been seeing people, these nonsensical blog posts like real bad misinterpretations of science, not really looking at any of the details of the study and the first time it came across as interesting of oh this is really cool looking at some of these details.

And again, that is just a bit of luck that nudges you in an appropriate area where you think actually, maybe I think these people who want to do it in this evidence based way seem to be more credible than what they've been listening to. Otherwise I could have ended up a Saldino fan.

Alan Flanagan: Yeah, that's it.

But I think that's the, what you said about, the exposure to academics in an educational context of, and hopefully people would get this if they're doing an undergrad and nutrition or dietetics as well perhaps to a lesser kind of magnitude of depth that you might get from an MSc or further.

But what I really noticed during my MSc was the commitment to presenting evidence. And this immediately leapt off the screen, anytime a lecturer was presenting and they'd have the reference and the graph, and they'd be describing like, this is what we've seen with this study.

It was a level of explanatory power that you didn't get from just listening to some random bro on underground wellness, and so I think if someone's got a mode to become of critical thinking ability, that immediately becomes obvious that this is a superior. Approach to this.

This is someone walking you through, not just, Hey, we've got evidence of this, but why it shows that and of course, then there's no substitute for actually then trying to apply that. And that's why formal education is so valuable because for me the quantum leap in my capacity for critical appraisal came during the MSc where after the first couple of modules where I was like, this was a new exposure for me not coming from a science background.

And I'd done okay. In those modules. Not great, not where I wanted to be. And it was having conversations with some of the, again, some of the people at Surrey and okay, this is where I'm at so far. This is the feedback I've got. What, how do I improve from. And I was probably lucky that I was good at writing and legal writing is similar to science writing in a different context.

So I had a transferable skill if I knew how to bring it over which thankfully I did. But again, it was that application that you have to do if you're doing an evidence based masters, right. As it's you have to read papers, you have to get better at pulling out. What's a good versus a bad paper.

And I think ultimately there's very little to no substitute for that. .

Danny Lennon: Yeah. I mean, if you think of any of those lectures where you could have someone talk about a set of studies or even a study, but the ability to ask them questions of, well, why do we conclude this instead of this with that for the sake of time, I think we better move to our next one, but hopefully that does a good enough job to, to answer that question.

The next question comes in from Tyson Brown, who asks:

"Apart from lowering salt intake and eating foods high in potassium. Are there other things you can take or do to reduce blood pressure?"

So in, in thinking about this I think there's distinct separate groups we can maybe talk about. One is change in actual body composition. Then we can look at dietary factors. Then we can look at exercise. And there be other things such as sleep or drugs.

So, at least to me and feel free to add in any gaps here, but I think we see quite clearly that weight loss, certainly within a certain range, probably 5-10% of body weight loss, particularly if someone has excess adiposity will reliably reduce blood pressure, probably visceral adiposity is particularly problematic here. So if we get a significant amount of weight loss that's gonna improve. And so that will drop blood pressure.

For a dietary component, I mean, there's probably a number of different ones we could get into detail, but we don't necessarily have to. There's probably on a pattern end, we could maybe talk about DASH diets and then on specific ends, we could think about like certain micronutrients or certain polyphenols and so on.

So I don't know which ones we wanna get into there. So maybe let's start with some of the dietary ones. What do you think is best to get into here beyond sodium and potassium?

Alan Flanagan: I think polyphenols are actually in terms of our current evidence and in terms of our mechanistic understanding of, and we've talked

about this on previous episodes, but for polyphenols, one of their main mechanisms of action that is believed to underpin their benefits on the cardiovascular system and the brain is improving cerebral vascular blood flow.

And they do this by influencing the nitric oxide enzyme system specifically inhibiting inducible, nitric oxide synthase and because excess nitric oxide is not necessarily a good thing. And then promoting through. Through the enhancement of nitric oxide, but in a well regulated way vasodilation or the dilation of blood vessels and increasing blood flow.

And we see that we see that in the brain with some of the mechanistic work on why they might have cognitive benefits, you see increases in cerebral vascular blood flow and ultimately then re reducing blood pressure. So I think as a specific nutrient, and obviously, in terms of, from a food based perspective, some of this might be.

You're getting everything for example, if you were to increase your intakes of potassium through different colored fruits and vegetables that's basically achieving the same thing. As far as polyphenol content goes and now actually we know that certain.

Based on the darkness of the pigment of a given fruit, like blueberries; that very dark purple pigment. We know that they're greater in concentrations of polyphenols and flavonoids. But I, for me I think it's probably their main, certainly the mechanism of action that we really have more concrete conclusions on evidence in humans, not just mechanistic, speculation.

So, yeah I think that I think that outside of the sodium potassium balance, then, flavonoid intake would be the, the next dietary step for me. I'm not sure if I'm missing something there.

Danny Lennon: Yeah. So, and again, people can reference that full episode we did on polyphenols and cardiovascular disease, which you get into much of those details within that.

We also have a, an episode around dietary nitrates, which may be relevant here and looking at some of the role of dietary nitrates here. And both those things in probably lend themselves to then a dietary pattern, like the DASH diet, where we do have quite a bit of evidence, but that's probably due to a number of those factors, right?

Not only are you restricting sodium, but you are promoting lots of colorful fruits and vegetables, which by nature, give these polyphenols, give dietary nitrate, et cetera. And so, and there's overall is a healthy dietary pattern that probably. Leads to weight loss in some people. And so there's multiple ways that it's probably leading to drops some blood pressure.

Alan Flanagan: I think calcium, we can tend to underappreciate calcium's role in, in blood pressure regulation as well through kind of calcium channels and all this kind of geeky stuff. But again the kind of the contribution of dairy and the low fat area in the DASH diet, and it's a kind of central food group in the DASH diet.

And I think that's probably making a contribution as well. So yeah, I think at that level that's for blood pressure, it's obviously the reference dietary pattern. And one of which we have enormous evidence for now from human intervention trials. There's potentially a role for mono and saturated fats.

As far as there, there is if the and a good example of this is the OMNI Heart trial, the OMNI Heart trial was really cool because one of the. The really positive things about the DASH diet is how modifiable it is. So the initial DASH intervention people have done multiple spinoffs, including, high red meat intake in the context of a DASH diet, the BOLD trial, for example.

But they, people tend to mis-cite that because they actually kept saturated fat at 6% of total energy intake. And people are like, oh, I see meat. It's yeah, bro. They were literally eating less saturated fat than anybody in the population. But the OMNI Heart trial did a kind of traditional DASH diet, the 50% kind of carbohydrate, the normal prescription.

It did a high protein DASH diet. That was two thirds plant, one third animal protein. And it did a high monounsaturated fat DASH diet where extro virgin olive oil was the primary added fat to bump total fat content up by increasing monounsaturated fat specifically.

And what was interesting in the OMNI Heart trial was both the protein- and the MUFA-enhanced DASH diets reduced blood pressure to a greater degree than the traditional DASH diet. But the monounsaturated fat diet seemed to actually have a slightly additive effect. Now again, it's probably the composite of its parts, because that MUFA rich diet still had higher dietary protein intake than the traditional DASH diet still how to focus on kind of plant proteins, two third plant, one third animal. So yeah, it's probably the total dietary pattern but still interesting as well. So yeah, I think there are a lot of different. Modifications

that someone could make. I don't think they need to adhere to that very initial, Sacks and colleagues 1992 DASH diet publication, right?

Danny Lennon: Yes. And even other healthy dietary patterns that fall outside that probably are doing a lot of the bulk of that work as well. That we'd see changes. So, so beyond then the diet, we have other things people can do lifestyle-wise of course, exercise is a pretty obvious one for physical activity generally.

And then actual exercise has been recognized for quite a bit of time. The interesting one is probably for quite a while, at least going back conventionally you'd have concerns around blood pressure and resistance training specifically because of the acute increases in blood pressure, you would get when lifting weights.

But we've now pretty strong evidence that strength training and resistance training actually can lead improvements in blood pressure. I think one of the sets of articles that are recommended on some of our previous episodes around exercise and blood pressure was done by our friend, dr. Austin Baraki who wrote about blood pressure and referenced some of the work there where you see the combination of strength training and aerobic training seems to lower blood pressure to a greater degree than either alone. But saying that for anyone to do any type of exercise is probably a good idea.

And there was one of the papers, I think that actually Jordan fenal maybe had linked to before it was a meta-analysis by Naci and colleagues so large meta-analysis 40,000 subjects in this. And they looked at the impact of exercise on blood pressure and found that there was a pretty direct comparison to certain antihypertensive drugs in patients with elevated blood pressure.

And so we have a pretty strong evidence base. It seems that exercise is good. And certainly if you can do a combination of those great, if not do something that you enjoy consistently and going from being sedentary to being physically active is probably gonna help drop blood pressure as well.

Alan Flanagan: Yeah, that's great news on the resistance training, because I I get like all these little burst capillaries in my eyes and around my eyes after Bracing with a belt. Yes. And I'm always like, "oh I'm going to have a stroke. Powerlifting will kill me". And then it's no, it actually, my blood pressure will lower apparently.

Danny Lennon: Beyond that, I think probably things like sleep-wise is probably screening for sleep apnea. If there's something that's a concern for you, if you got that fixed, it's probably gonna reduce your blood pressure. And then things that we don't need to get into detail here, but of course drugs are gonna drop your blood pressure as well.

So there's a combination of many things there. So I think as a quick recap.... Stress.

Alan Flanagan: Yeah. Don't look at the news because it's constant stress. Get offline.

Danny Lennon: Yeah. With that, maybe to recap some of the things we just mentioned there fat loss, particularly loss of visceral fat is probably beneficial.

So if someone has excess adiposity losing more than 5%, maybe even more than 10% of their body weight is probably gonna drop blood pressure changes in diet. So we have polyphenols particularly could be useful here dietary nitrate, and then an overall dietary pattern. That includes that. So lots of different fruits and vegetables whole grains low sodium, low saturated, fat, et cetera.

Exercise is a good idea. And then potentially getting screened for things like sleep apnea, or if there is some other undiagnosed medical condition that is causing your blood pressure, it's probably worth finding out what that is. So if you are measuring your blood pressure at home and it's high, go to your doctor don't just think I'll just drink some red wine for the polyphenols.

And that is good enough. That is not our word of advice. Let's get to another question. Martin Glynn asks:

"what is the best ratio of DHA to EPA in order to increase my omega three index, which is currently at five?"

Alan Flanagan: With the O3I we typically see certainly the observational research really more strong risk reductions where it's 7% to 8% or more. So doing very well at five. Nevertheless one thing and we discussed this before on the episode and whether someone needs a direct source of DHA is that fundamentally the omega three index primarily reflects DHA. Right. And this is because, it's looking at red blood cell red blood cell fatty acids.

And just because of their kind of differing metabolism we tend to get higher concentrations of DHA in, in actual, cell and red blood cells and EPA

sometimes can be more in, in the circulation. But it's primarily reflecting DHA status. And so ultimately, I don't know that one has to micromanage what's my ratio of DHA to EPA. The population research is often just looking at people that have food based intakes of long chain omega-3 fatty acids, fish in particular. So I would just say eat oily fish and probably oily fish that is more dense in terms of its enrichment with these long chain omega-3 fatty acids.

So I would be thinking mackerel, salmon, sardines, herrings those kind of foods. And yeah, I mean, depending on what your frequency of oily fish intake is currently that could be maybe something to look at increasing But that would be I think taking a food first approach and not necessarily worrying about micromanaging ratios of DHA to EPA.

Danny Lennon: I couldn't really find anything on like specific comparisons of different ratios and different outcomes per se. There was a one crossover trial here that I found Allaire and colleagues. So double blind control crossover study about 150 people in here. And they had three different treatment phases that everyone went through.

One was either 2.7 grams per day of EPA, 2.7 grams per day of DHA, or then a placebo of three grams of corn oil. And so you have everyone does each of those there's nine week wash washout period in between. And they found that the increase in the omega three index after supplementation was greater with the DHA than with the EPA.

So increase of 5.6% compared to the control. Whereas the EPA was plus 3.3% compared to control. So both importantly here are increasing it. But they're just more with the DHA, which speaks to the point that you actually said. And then one other thing that I did see reference that might be of use to address your question, Martin, that on the Omega Quant website.; So they obviously do some testing around this; they have a kind of informal omega three index calculator there where you can put in your current omega three index and it your target one and it spits out an average intake of combined EPA and DHA, that would probably get you there.

And it's based on a published paper from Walker and colleagues 2019, which, which modeled this out based on data that they had. And they tried to find on the average changes we're seeing from different supplementation and food based interventions. Can we get a model? How much of the combined EPA DHA would increase your omega3 index per unit.

And so you can put those figures in, it'll give you a rough estimation. So for example, this model from that Walker and colleagues paper predicted that the final omega3 index for with a baseline concentration about 5%, which was the average in that cohort, if you gave them 850 milligrams a day combined of EPA and DHA, that would leave them with an omega three index of 6.5%.

And so then you go higher dose. Obviously, if you want 8% all of this is to also say that there's considerable variation that we see between people yes. In the response to supplementation. So these are not exact figures that if you do this is what your omega three index is gonna be. More importantly is probably what.Alan has actually said of if your omega-3 index is below where you would like it to be, and you increase your intake of ideally EPA and DHA containing foods and, or then supplements if that's not possible. And then increase that to a point where when you retest it's back up to a level you want, and that's probably the best when individual you're gonna get up.

Alan Flanagan: Yeah. And the thing is five is probably fine. I mean, where we typically see, like the kind of the inverse, the comparisons or the potential part is when it's less than two to three So five is probably fine. I did actually, just when you were describing those interventions, then think, well, I actually don't know what Martin's diet is.

So I didn't mean to make an assumption by just saying here, go and shovel mackerel in. So if that's the case, then obviously, an algae based supplement is obviously available if Martin does consume a plant exclusive diet, then you know, this is obviously attainable through supplementation as well.

And some of those ratios that Danny mentioned or supplemental doses dosage ranges might provide a guide then, because I do know that the supplements tend to be they tend to have really good DHA levels actually, but they might, in terms of their per dose level it might need a little bit more to reach some of those maybe levels that were used in some of the trials.

Danny Lennon: Perfect. So hopefully that helps you, Martin. We will link up to any of the things that we just mentioned there. If you want to go and check those out. So the next question I think this is one that you will indeed find fun if it's talking about mechanisms of changing LDL, which I know is a fun one for you.

This comes in from Jessica Pfundson and she's asking about statins versus ezetimibe:

"What are the differences between the two? Mechanism of action? Are there situations, conditions, genetic markers, which one may work better than the other?"

And so just for some clarity, for other people listening, statins and ezetimibe are of course, classes of drugs that lower LDL cholesterol and apoB-containing lipoproteins.

And so this reduction is obviously aimed at reducing risk of atherosclerotic cardiovascular disease. So with that, these drug classes, statins, and ezetimibe, Alan, can you walk us through what are the differences between the two and what are the differences in those mechanisms by which they lead to these reductions?

Alan Flanagan: Yeah, so the difference between the two is their mechanisms; is what are they both targeting? So we know that if we're going to lower the level of cholesterol in atherogenic lipoproteins of which LDL is the most predominant in the circulation. Then what we need is we need the LDL receptor to be expressed and we need it to be expressed in sufficient numbers that can deal with the level of cholesterol being transported in lipoproteins LDL, specifically through the body.

And so when we have cholesterol levels, blood levels of it, of cholesterol, primarily stored in LDL carried an LDL that are within certain lower ranges. And we don't have a genetic defect in the production of the LDL receptor, like familial hypercholesterolemia, we'll have a situation where the LDL receptor can sufficiently take up that cholesterol that LDL is bringing around and remove it from the circulation.

And total cholesterol levels then come down, LDL cholesterol levels come down. The problem is when we get over certain thresholds and the LDL receptor can't keep up with the level of cholesterol that needs to be cleared from the blood. So the unifying mechanism here is increasing expression of the LDL receptor, such that we can clear that cholesterol that's being transported in LDL.

And that happens through a number of ways. And one way in which it happens is if we either lower the synthesis of cholesterol in the body itself or we decrease the cholesterol pool, and this is a pool of cholesterol that's recycled in the liver. And it's often using the hepatic portal vein.

It can be basically eliminated through that pathway where it binds to bile and is eliminated from the body. And that's often achieved when we've got a high fiber

diet as well. And so what happens in that context is the cholesterol pool comes down and the body senses, well, hold on a minute, we've our internal cholesterol stores are lowering.

So we'll upregulate expression of the LDL receptor. So it will take in more cholesterol into cells. So that's the unifying way in which both of these drugs will lower LDL cholesterol levels, but they'll do it through different mechanisms. So statins will target an enzyme known as HMG CoA reductase, and HMG Co-R basically is a pathway that leads to liver synthesis, endogenous internal synthesis of cholesterol. And by inhibiting that enzyme statins decrease the ultimate synthesis of cholesterol, which in turn, then lowers the pool of available cholesterol, which leads to an upregulation of the LDL receptor. And we clear LDL from the blood.

Ezetimibe targets a different pathway is ezetimibe targets a transporter in the gut, in the intestine known as NPC1L1. And NPC1L1 is a transporter that is involved in the absorption of dietary cholesterol. And we don't absorb huge amounts of dietary cholesterol, but the cholesterol that we do absorb has an influence on then the availability of cholesterol in this cholesterol pool.

But NPC1L1 also is involved in this conversion process, this recycling cholesterol process that I mentioned in terms of the sequestering of cholesterol by bile acids. So ezetimibe as a drug actually targets this intestinal level. So statins are targeting cholesterol synthesis pathway to the liver.

Ezetimibe is targeting the intestine and specifically is targeting intestinal cholesterol, absorption, and also increasing the conversion of cholesterol in the liver to bile acids. And the elimination of cholesterol through that pathway. And when it does that, and it does that by binding to that transport or protein NPC1L1, and that inhibits that cholesterol absorption from the diet, from the gut and that it also does it by increasing the conversion of liver cholesterol to bile.

And again, that has the effect of reducing the endogenous cholesterol pool, increasing up regulation of LDL receptor and leading to greater clearance of cholesterol in from LDL lowering, LDL cholesterol in the blood. And so that's essentially the difference in their mechanisms of actions in terms of indications.

The main difference is the magnitude of LDL lowering that is achieved. So because the pathway that I described for ezetimibe the NPC1L1 pathway generally, and biasses, it's not. At the same magnitude. So for example, we mentioned dietary cholesterol. We don't really have a huge amount of absorption.

So ezetimibe of the three available classes of drugs that we have. And there's also, PCSK9 inhibitors. There's a kind of order of magnitude to how low LDL can be achieved with these drugs. And PCSK9 inhibitors have generally the largest effect and statins can, particularly if they're high intensity, statins can achieve very large reductions in LDL cholesterol, and ezetimibe typically achieves more modest reductions in LDL cholesterol.

are there situations where their indication for use might differ? I mean, for someone with modestly elevated LDL cholesterol levels, it's possible that they could achieve a net reduction from just using ezetimibe. But our current treatment recommendations are to begin people on a statin initially.

And then if they're not achieving a certain target of LDL cholesterol with just the statin alone they might start someone on a kind of moderate or intensity dose. And they might first increase that to a higher intensity statin treatment. And then if they're still not achieving, they might add ezetimibe to it, to use as a combination therapy in order to get LDL down.

And so, for example, The IMPROVE-IT trial was a trial in about 19,000 participants. They already had coronary syndrome. They were secondary prevention patients. And what this trial did, was it compared a statin on its own. So statin monotherapy to a statin with the addition of ezetimibeand that reduced LDL by an additional 0.4 mmol/L, and an additional, nearly 7% reduction in risk of cardiovascular events compared to just statin monotherapy alone.

And there are other intervention trials again, where the combination of statin plus ezetimibe has achieved a relative risk reduction that is similar to the magnitude of risk reduction observed with just statins alone. If you achieved the same magnitude of LDL lowering. And so this is one of the really important points here is that the reduction in cardiovascular disease risk and events is proportional to LDL lowering.

So the indication for use of ezetimibe in this context would be whether someone actually needs it to achieve that additional net reduction. And some people may not, they may actually achieve a certain target for treatment, just using statin monotherapy. You could have situations where people are using statins and ezetimibe, and still haven't reached targets for treatments.

And if they're secondary prevention, they'll then add a PCSK9 inhibitor to really Jack that LDL cholesterol down to as low as 30 milligrams per deciliter. But as far as the genetic aspect, I mean, there. Individuals that have genetic variants in

NPC1L1 that actually lead to lifelong, lower cholesterol levels and they have lower heart disease risk.

It's not as low as if you had a variant in PCSK9, because you've just looked in then at that point and you have the lowest levels of cholesterol and heart disease rates. But as far as where one may work better than the other, ultimately statins do have a more profound effect on their own and lowering LDL.

A high intensity statin, like something like an 80 milligram dose of atorvastatin is going to have a really big impact on lowering someone's LDL cholesterol levels to the level that ezetimibe wouldn't achieve if you just took it on its own. So as far as quote, better, better here would be magnitude of lipid lowering statin's overall would be the preferred option, but ezetimibe really does serve a purpose as an additional adjuvent therapy to help people get to these net reductions in LDL that will lower their cardiovascular.

Danny Lennon: So I'm gonna move to another question that I think is distinctly gonna be best answered by yourself, given that you have a PhD. And I do not this question comes from Kate who asks:

"Hi, first of all, I wanna thank you so much for the whole podcast, which I'm really looking forward to."

Thank you so much.

"I have one question for you. I'm starting a PhD in the fall concerning the pathophysiology of metabolic diseases, and I'd like to take some courses that would help me in my research. Since you're in contact with a lot of specialists from different institutions, you probably have more insight than I do into what the possibilities are, would you have any recommendations or an overview of courses related to metabolic diseases or even methodology and statistics that could help a beginner scientist? Thank you very much."

So with that question, Alan, for someone starting a PhD, interested in picking some courses in this area, what ones do you think might be worth putting on the radar in terms of your own skill sets?

Alan Flanagan: One website there's two, actually that I have found incredibly useful for statistics is one is called Statistically Speaking and that's run by US statistician called Karen Grace-Martin, and that's a membership website. But it's incredibly, they have a whole learning platform. There's a whole process of stepwise incremental program that you can go through to up skill on statistics.

And so I highly recommend that the website's called the Analysis Factor. The subscription platform they have is called statistically speaking. It's been incredible to learn, and also it has a kind of mentor group. They do webinars on specific statistical topics. They have the ability to ask Q and As in a forum and they're all statisticians there.

So that is in invaluable resource in my opinion. And then there's also layered statistics. Now that is, if you specifically use SPSS as your stats platform, SPSS layered statistics will have these guides on, let's say you need to do a multiple linear regression. It will have guides on how to set up your data, how to run. And check assumptions that you are meeting for that statistical test to be valid, how to interpret that data. And so when you're learning a new stats software, It can be quite intimidating. And something like this layered statistics is invaluable in taking a lot of that intimidation out of the way and feeling like you've got essentially, which you do from their guides, a walk step by step through, how to run that particular statistical test in SPSS.

And ultimately get to the point of writing it up. So they would be my two kind of stats recommendations.

Danny Lennon: The next question comes in from Christine Wieser. She asks:

"Is astaxanthin a good substitute for algae oil, for someone who follows a vegan diet?"

So at least the way that I took this question or the presumption I'm basing on of why Christine is asking this is that in our episodes around getting a direct form of DHA being a good idea, and therefore for people on a vegan diet we've of course talked about the potential use of using an algae oil, because that does indeed contain DHA.

Now where astaxanthin comes in is that this is something that is contained within algae oil and also in things like krill oil as well, but in and of itself is not necessarily the same. It's a specific retinoid. So a responsible for that kind of red dietary color that you may see in certain things.

And so has in itself potential to have impacts. And because it is this important caretnoid that has potentially metabolic impact, but itself is not something that is containing the DHA. And so the basis of our recommendation for someone on a vegan diet to consume algae oil is to provide a source of DHA that you are otherwise not getting directly.

And whilst astaxanthin could be contained in this in itself is not providing that, that DHA it's a separate component of that aisle. And so is going to not be doing that job. It could be doing other things, but is not going to be increasing someone's DHA intake. So at least that's the way I picked up the question.

I dunno if you've any other additional thoughts on that?

Alan Flanagan: No, I think that's, I think that's exactly it.

Danny Lennon: Going to go to a question from Ekaterina who asks:

"Do you have any suggestions of how to better manage hunger in obese women with PCOS any specific nutrition or lifestyle recommendations? Thanks a lot in advance."

Alan Flanagan: Yeah. So it's complex in the sense that, obviously the pathophysiology of PCOS is complex and there are different phenotypes. But one thing that does appear to be known at this point is that there, there is a higher level of hunger and appetite in women with PCOS.

That may relate to the impact of and one, one of the aspects of the pathophysiology of PCOS is dysfunctional hypotheic pituitary, adrenal, and ovarian access function. So HPA-axis function. And this could also, as part of, we tend to think of this then as far as the downstream effects and on, on the ovaries, on ovarian function, but it may also influence the hypothalamus, obviously in terms of leptin as an energy balance regulating hormone and grehlin as well.

And there, there is obviously, that there's other factors potentially going on, but we could typically say that, there, there is a common potentially higher levels of appetite dysregulation in women with PCOS. So there, there actually is some interesting research in this regard that I think might actually help.

There was a paper by Jakubowicz and colleagues, Daniela Jakubowicz and that group, which looked at front loading energy intake in women with PCOS. So they did they've done a number of interventions looking at kind of energy distribution where they've compared high energy breakfasts to high energy dinners and low energy breakfasts.

And this is interesting because there potentially maybe a role for hunger regulation across the day and a suppression as far as even objective measures like ghrelin. So they've some research where basically in women with PCOS

front loading energy intake has had beneficial effects even on some of the metabolic outcomes.

But particularly on, in the context of a hypo caloric diet as well, a weight loss, inducing, diet suppressing grin. And what they found was that even after the intervention was over that there was a there was a persistent effect on the suppression of ghrelin from front loading and having high energy protein and fat rich breakfasts. So that's one potential strategy. There is also the kind of combination of increasing dietary protein combined with low glycemic load carbohydrate choices. And that maybe another factor we don't necessarily know whether there'll be a specifically an impact on ghrelin necessarily as an outcome.

But there is some potential research, obviously wider research on high protein diets and satiety. And some of these interventions. Have been looked at in in kind of women with PCOS and there is mixed findings in relation to this. And that actually might just reflect if the, the, the different phenotypes with polycystic ovarian syndrome.

So I, I would say that one potential strategy that could benefit factoring in some of this evidence is high energy intake early in the day, but specifically focusing on a kind of high protein and low GI carbohydrate. High energy breakfast or energy intake early in the day.

And that may be something that has an impact on appetite regulation, not just over the course of that day, but potentially over the longer term in the context, if that was a consistent behavior in the context of, in a weight loss diet

Danny Lennon: I think we'll do one more question and that will round us out for the day.

This question is almost directly and perfectly written for you to answer. I think this comes in from Melanie Yelland, who says:

"hi Sigma team. I was wondering if you had any recommendations for anyone wanting to get involved in chrono nutrition research as this is an evolving area. There aren't always direct education paths, example and master's program available everywhere. Do you have any recommendations program recommendations that you suggest to people who are looking to get their foot in the door for opportunities in this area? "

So with this Alan given that you have done your doctoral degree in this area of research what kinda suggestions might you give to someone who's looking at this as something that they're interested in maybe wants to get involved formally? What potential options are for getting into this as a research field?

Alan Flanagan: Again, I think the thing to do is to look at sites like for example, find a PhD or or otherwise if that's the level that they're at, I think they did mention masters as well. But again, I think relative to where you are in the world finding researchers in that area.

And by all means here, please feel free to email me and I can, recommend a few names if you're, if you're based in the UK, for example, it depends on, the group, obviously, in terms of where you are, is there direct education paths that also gives me an indication that maybe you're in the states generally here a masters would be more general and not necessarily chrononutrition, masters.

And then that obviously would tee up going into something more specialized in the context of a PhD. So, you're correct to say that there aren't always direct education pathways. But there certainly are plenty of research groups in this area. It's a growing aspect of nutrition research. There's a couple of really great groups in the states.

There's some great groups in the UK. And so it, yeah it depends there, there are some great groups on the continent. So again, it's that idea of whose research do you read in this area? And, reach out to them and see maybe what they've got going on. Are there new projects in the pipeline?

It might relate obviously then to what stage you're at yourself in terms of the kind of higher education pathway. But yeah, by all means, just feel free to send me an email and and we could have a bit of a brainstorm and you can maybe let me know where you are in the world and I can maybe suggest a few names.

Danny Lennon: Cool. Yeah. Yeah. I think certainly it makes things easier if it's at the level of looking for doing a PhD or even beyond that, if someone has a PhD is looking to do postdoc work, you obviously have labs that are doing this type of research and to reach out. I think one thing that I might put on someone's radar, if they're... but maybe they're looking at either doing an undergraduate degree or a master's degree with their goal in mind of, oh, I would love to eventually get into chrono nutrition. Research is a as Alan mentioned, you don't necessarily have to start out with a very specific chrono nutrition focus, certainly at undergrad and certainly masters because you, you won't find those anyway.

And then it's also worth thinking what area of this research are you most interested by? Because as I'm sure Alan, you can talk about, there are people doing research in this field have a wide variety of backgrounds where you have people with very much a nutrition background. You have others with very much on the kind of circadian biology background, some coming from neurobiology.

And they all have these different levels of expertise related to circadian rhythms and chronobiology, and then it ends up being some of their projects and some of their research. End up being, looking at meal timing. And so with that in mind, if someone is going into maybe looking at a master's program or undergraduate degree, you can maybe look at well, what other kind of related fields are there?

Is there a group that is doing a nutrition masters, and maybe that's a good Institute where there's maybe meal timing, research going on, or maybe it's neurobiology that you're more interested in other people at doing research involved in light and circadian rhythms. And they would be teaching on your master's course. They might be ways to indirectly get exposure to that before you specialize at a later time point.